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ANTI-EMETIC DRUG EFFECTS ON PERFORMANCE PHASE I: LABORATORY STUDY

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The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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The objectives of this study were to evaluate the effects of two anti-emetic drugs, granisetron (@ 2 mg p.o.) and ondansetron (@ 8 mg p.o.) on basic cognitive skills and complex task performance. The experimental approach, involving 24 active-duty, military subjects was a placebo controlled, double blind, crossover design with a positive control (prochlorperazine @ 10 mg p.o.) condition. Testing was accomplished during the evening and early morning hours, between 1630h and 0230h. Therefore, fatigue stemming from an extended work period and a disrupted work/rest cycle was also part of the study design. Data were collected on cognitive and psychmotor effects, affective state changes, temperature, drug - serum levels and side effects. The drugs of interest, granisetron and ondansetron, were extremely well tolerated and with no obvious side effects when compared to the placebo condition. Two of five cognitive tests detected a positive control effect and nearly all of the measurment instruments demonstrated a fatigue effect. There was no evidence of any cognitive, psychomotor or subjective state changes caused by either granisetron or ondansetron.

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ABSTRACT

The objectives of this study were to evaluate the effects of two anti-emetic drugs, granisetron (@ 2 mg p.o.) and ondansetron (@ 8 mg p.o.) on basic cognitive skills and complex task performance. The experimental approach, involving 24 active-duty, military subjects was a placebo controlled, double blind, crossover design with a positive control (prochlorperazine @ 10 mg p.o.) condition. Testing was accomplished during the evening and early morning hours, between 1630 h and 0230 h. Therefore, fatigue stemming from an extended work period and a disrupted work/rest cycle, was also part of the study design. Data were collected on: cognitive and psychomotor effects, affective state changes, temperature, serum-drug levels and side effects. The drugs of interest, granisetron and ondansetron, were extremely well tolerated and with no obvious side effects when compared to the placebo condition. Two of five cognitive tests detected a positive control effect and nearly all or the measurement instruments demonstrated a fatigue effect. There was no evidence of any cognitive, psychomotor or subjective state changes caused by either granisetron or ondansetron.

PREFACE

This report documents work performed for the Armstrong Laboratory under prime contractor, Systems Research Laboratories (contract F41624-91-C-2003) in collaboration with co-investigators from the Sustained Operations Branch of the Armstrong Laboratory. Medical monitoring support and analysis of symptoms data were provided by the Aerospace Medicine Department of the USAF School of Aerospace Medicine.

The formal requirement for this research is documented in a NATO Project Group 29 statement of work for the selection of a drug for the prevention and treatment of radiation induced nausea and vomiting. Funding for the effort was provided by the Defense Nuclear Agency (DNA), through the U. S. Army Nuclear and Chemical Agency.

Several individuals deserve recognition for their contributions: Dr. Samuel G. Schiflett of the Armstrong Laboratory for providing expertise in the area of drug effects on complex military task performance; Mr. Joe Fischer and Mr. Dan Bauer, also of the Armstrong Laboratory, for experimental design, data analysis and interpretation; Dr. Douglas R. Eddy, NTI, Inc., who provided critical review of the experimental design and results interpretation and Ms. Rebecca Cardenas for assisting with subject training; Dr. Marty Javors, University of Texas Health Sciences Center, for performing the serum-drug assays; Dr. Bob Young, formerly with the DNA, and Mr. Rob Kehlet of the DNA for their confidence in this laboratory and their project recommendations. Finally, the authors wish to acknowledge the contributions of Dr. Greg Trafton, Dr. Jerry Chubb and Mr. Joe Campbell to the design and demonstration of a synthetic task for assessing operationally relevant, complex task performance.

ANTI-EMETIC DRUG EFFECTS ON PERFORMANCE
PHASE I: LABORATORY STUDY

1.0 INTRODUCTION

1.1 Study Objectives - The objective of this study was to evaluate the effects of standard doses of two anti-emetic drugs (granisetron and ondansetron) on the cognitive and psychomotor task performance of active duty military subjects. Efficacy of the selected treatment drugs has been demonstrated against radiation induced emesis and these drugs were not expected to produce aeromedically significant side effects. This study compared the two candidate anti-emetic drugs (granisetron and ondansetron) against a positive control drug (prochlorperazine) and a placebo through the collection of cognitive, physiological and subjective effects under single dose treatment conditions. Testing was accomplished during the evening and into the early morning hours. Therefore, fatigue, stemming from an extended work period and a disrupted work/rest cycle, was also part of the study design. A tertiary objective was to develop a synthetic analog of a "real world" operational task, and to demonstrate the sensitivity of this analog against standard cognitive and psychomotor performance tests

1.2 Target Drugs - The target drugs for this study (granisetron and ondansetron) were selected based on their established function as competitive antagonists at 5-HT3 receptor sites. A widely supported theory of radiation sickness suggests that cellular damage and necrosis elicit the release of serotonin (5-hydroxytryptamine or 5-HT) from the enterochromaffin cells of the intestinal mucosa. This in turn activates 5-HT3 receptors along vagal afferent pathways ultimately stimulating the chemoreceptor trigger zone (CTZ) and vomiting center (VC) located in the brain stem. Radiation may also result in direct stimulation of 5-HT3 receptors in the CTZ and VC to produce vomiting. (Aapro, 1991; Andrews, 1988; Barnes, 1990; Freeman, 1992; Harding, 1988; King, 1991; Rabin, 1992; Seynaeve, 1991).

1.3 Requirement - The formal *requirement* for this research stems from a NATO Army Armaments Group, Project Group 29 (PG-29) statement of work for the selection of a drug for the prevention and treatment of radiation-induced nausea and vomiting. The work described herein represents a part of research efforts in four NATO member nations participating in PG- 29. Sponsorship and resources are derived from the Defense Nuclear Agency (DNA). The requirement for this work was approved by the USAF/SG.

Incapacitation resulting from nausea and vomiting incidental to sudden or accumulative exposure to ionizing radiation is a probable consequence of nuclear weapons use. In spite of efforts to prevent the spread of nuclear weapons, the use of such weapons in theater conflict or by terrorists continues to represent a potential threat. Although the nuclear armed, ballistic threat is greatly diminished, strategic or theater forces could be on the receiving end of an enemy first strike and/or it may be necessary to launch second strikes against targets in proximity to previously detonated nuclear weapons. Moreover, conventional weapons could result in the detonation of underground nuclear storage facilities and nuclear fratricide or enemy launch mishaps could result in hazardous levels of radiation exposure to air and ground forces.

Currently, there are no immediately available anti-emetic drugs for use by operational aircrew to protect against radiation induced nausea and vomiting. The results of this study were expected to provide scientific evidence relevant to the selection of anti-emetic drugs for field simulation testing and future operational use. In addition, the laboratory study was designed to provide a scientific basis for an efficient and valid field simulation test, recognizing the cost of aircrew downtime and simulator use. Performance measures that are operationally appropriate and sensitive to drug effects could be selected for field testing. The need to test all of the aircrew participants against a positive control could be evaluated and the requirement for a prolonged mission scenario to assess the possible interactive effects of fatigue with an anti-emetic drug could be determined. Without studies to evaluate the side effects and safety of anti-emetic drugs before a drug is fielded, aircrew will remain vulnerable to possible drug induced performance decrements and/or incapacitation from radiation induced nausea and vomiting .

1.4 Summary - This investigation studied volunteer subjects exposed to anti-emetic drugs of reasonably well established pharmacokinetics, side-effects and dose-dependent action. Performance measurement employed cognitive and psychomotor tests expected to be sensitive to drug effects (NATO AGARD, 1989; Perez, 1987; Reeves, 1991; Schlegel, 1995). Physiological and subjective effects data were collected over an extended activity schedule. A synthetic task methodology (Marshall-Mies, 1993) was used to develop a task that represented an analog of the functions performed by the B-1B Defensive Systems Officer (Trafton, 1995). This synthetic task was evaluated against standard measurement tools for sensitivity to drug induced performance changes.

2.0 METHODS

2.1 Experimental Design - This study was based on a within subjects, repeated measures design for two anti-emetic drugs, a positive control drug and a placebo, under single dose treatment conditions. Exposure to the four treatment conditions was counter-balanced for order effects and data collection was conducted under double blind conditions, **Table 2.1-1.**

Table 2.1-1: Repeated Measures Design

Test Day	1		3		5		7
Wash-out Day		2		4		6	

Order Group	Drug		Drug		Drug		Drug
Grp. I	Ondansetron		Granisetron		Placebo		Prochlorper.
Grp. II	Granisetron		Prochlorper.		Ondansetron		Placebo
Grp. III	Placebo		Ondansetron		Prochlorper.		Granisetron
Grp. IV	Prochlorper.		Placebo		Granisetron		Ondansetron

Drug Treatment: n = 24
Order Effects: n = 6

2.2 Subjects - Twenty-four subjects were selected from a group of active duty military volunteers. Because of anticipated age related differences in the uptake, distribution and metabolism of the target anti-emetic drugs, the subject population was restricted to an age range of 18 - 35 years. Subjects, in fact, ranged in age from 19-31 years with a mean age of 24.96 yr. Individual weights were distributed between 125 and 210 lb with and average of 171.67 lb and heights varied between 62 and 76 in. with a mean of 68.79 in.. In general, demographics were representative of the active duty United States Air Force population in such factors as: officer / enlisted, males / females, and Caucasians / minorities. There were 5 officers (21%) and 19 enlisted (79%) ; 20 males (83%) and 4 females (17%) ; 18 Caucasians (75%) and 6 minorities (2 African-Americans, 3 Hispanics and 1 Oriental for a minority population of 25%), **Table 2.2-1.**

Table 2.2-1: Subject Characteristics

n=24	Age	Weight	Height	Male	Female	Officer	Enlist	Cauc	Non-C
Subjects				20	4	5	19	18	6
Percent				83%	17%	21%	79%	75%	25%
Mean	25yr	172lb	69in						
Range	19-31yr	125-210	62-76in						

In matters of life style, subjects were asked to decline participation if they ingested, an average of more than 5 caffeinated beverages per day (coffee and sodas in any combination; normal quantities apply i.e. 1 cup of coffee = 8 oz and 1 soda = 12 oz) and/or smoke more than a pack of cigarettes per day. Based on a life style questionnaire, 6 subjects (25%) used tobacco (5 smoked cigarettes averaging 0.6 packs per day and 1 used smokeless tobacco an average 5 times per day); 18 subjects (75%) used caffeine (averaging 1.84 cups/cans per day) and 12 subjects (50%) used alcohol (averaging 1.67 drinks per day). As a condition of voluntary consent, subjects were asked to adhere to alcohol and caffeine restrictions during the study. The alcohol restriction was no more than two alcoholic beverages in any one day during the study and no alcohol within 12 h. of any test session. Subjects also agreed to refrain from consuming more than 5 caffeinated beverages (coffee and sodas in any combination) per day during the test week. Subjects were prohibited from using nicotine, alcohol or caffeine during the test data collection periods. Based on scientific interest in fatigue and circadian dyschronization, together with possible drug / circadian phase interactions, information on each subject's sleep habits and quality were also surveyed. This subject population averaged 7.06 h. of sleep per night with an average of 1.33 awakenings. Only 2 subjects (8%) reported taking short duration naps on a regular basis. Sleep quality was reported as generally excellent and averaged a rating of 1.33 on a scale of 1-5 with 1 being the best possible rating, **Table 2.2-2.**

Table 2.2-2: Life Style Factors

n=24	Tobacco	Alcohol	Caffeine	Sleep	Awaken	Naps	Sleep Q[1]
Subjects	7	12	18			2	
Percent	29%	50%	75%			8%	
Mean				7.06 h	1.33/night		1.33
Range				5.5-7.5 h	1-2/night		1-2

[1] Sleep quality scale (1= usually restful and deep *to* 5= chronic sleeplessness)

Subjects were required to be in good health and to have a current physical examination (without waivers) on record. All subjects were screened for allergies, current and previous (within 6 months), use of prescription medication, and any history of adverse reaction to drugs and, in particular, the classes of drugs used in this study. Each subject was required to have a negative Human Immunodeficiency Virus test within one year previous to the start of the study. Female subjects were required to affirm to the best of their knowledge: not being pregnant, trying to become pregnant, and, if sexually active, the use of a reliable form of contraception. Female subjects were required to submit to a pregnancy test within 3 days of the start of data collection.

Subjects were pre-briefed on study objectives, methods and possible drug side effects. Subjects were advised of the sedative effects of the positive control drug and infrequent occurrences of extrapyramidal events. Subjects were also advised to refrain from consuming alcohol, driving or operating machinery for a period of at least 12 h following the administration of the treatment drugs. Subjects were also informed of the most frequently occurring side effects of the target drugs i.e. headache and constipation. Information describing precautions related to the use of each drug was also made available to the subjects. A drug effects questionnaire was administered at regular intervals during the data collection periods and between experimental trials. Subjects were advised to consult with the study team medical officer for any symptoms rated moderate to severe which occurred at any time during the study and for a period of 24 h after the last experimental trial. The stopping rule was explained so the subject could, at any time, elect to discontinue participation. The medical monitor could also, independently, stop a subject from participating or break the pill-dose/subject-session code. The Brooks AFB Command Control Center also had a copy of the code which could be broken if a problem were to arise.

A study team physician was immediately available in the test facility throughout each of the subject instrumentation and data collection periods. Other team investigators either performing or assisting in the performance of medical procedures were properly trained and under the direct supervision of the study team physician. The Crew Technology Division's Chief of Aerospace Medicine was responsible for developing the monitoring and evaluation criteria appropriate to the conduct of medical procedures employed in this study and for reviewing emergency procedures for adverse reactors. A medical "crash cart" was relocated to the immediate vicinity of the subject test area.

Each subject signed a voluntary consent document containing the understanding they could withdraw consent and discontinue participation in the study at any time without prejudice. Each

subject received one hundred dollars per completed test session and a total compensation of four hundred dollars. The 24 original subjects completed all training and test sessions.

2.3 Treatment Drugs - This laboratory study evaluated two anti-emetic drugs and a positive control drug administered in oral, capsule form at commonly prescribed dose levels. The drugs were: (a) granisetron p.o. @ 2-mg, trade name Kytril, supplied by SmithKline Beecham, (b) ondansetron p.o. @ 8-mg, trade name Zofran, supplied by Glaxo (Granisetron, 1991; Zofran, 1993), and (c) prochlorperazine @ 10-mg, trade name Compazine, supplied by SmithKline Beecham. Ondansetron is available by prescription for administration in both oral and i.v. forms for use as an anti-emetic in treating chemotherapy patients. Oral granisetron was approved, during the course of this study, for the mitigation of chemotherapy induced nausea and vomiting. Prochlorperazine is an approved anti-emetic, tranquilizer and anti-psychotic drug. For this study, both of the target drugs and the positive control drug were granted an Investigational New Drug (IND) status by the Food and Drug Administration (FDA), IND # 44,675, dated 3/7/94, since the focus of this study was outside of the normally prescribed clinical uses for these drugs. Approvals for this study were also granted by the HQ AFMOA/SGPT Institutional Review Board, SGO # R94-025, dated 5/31/94 and the Armstrong Laboratory Committee on Human Experimentation , ACHE # 94-02, dated 8/5/94.

2.3.1 Granisetron - Granisetron (trade name, Kytril, mfg. SmithKline Beecham) is a competitive serotonergic antagonist exhibiting great affinity for 5-HT3 receptor sites (Plosker, 1991). This drug has been studied extensively in animals and humans and is a well-tolerated and effective anti-emetic agent in radiotherapy-induced emesis (Hunter, 1991; Logue, 1991; Seynaeve, 1991). Granisetron is widely prescribed throughout Europe for the prevention of emesis caused by cytotoxic and radiation therapies. Granisetron, as an anti-emetic therapy for cancer patients undergoing chemotherapy, has recently been approved by the FDA. Granisetron is a potent and selective 5-HT3 receptor antagonist which has beneficial therapeutic effects in the treatment of radiation induced nausea and vomiting. Studies of granisetron in healthy volunteers have shown the drug to be well tolerated in single doses of up to 300-μg/kg i.v., a dose more than 7 times in excess of the 2-mg dose proposed for this study. With repeated dosing of granisetron for up to seven days, there was no evidence of an effect on pulse rate, blood pressure or ECG parameters (Upward, 1990). There is little evidence to suggest that Granisetron has any impact on EEG, psychometric or psychomotor performance (Leigh, 1991; Leigh, 1992). No extrapyramidal reactions have been reported (Seynaeve, 1991). The most common side effects are headache and mild constipation which normally resolve without intervention. In a study of healthy volunteers, none were able to differentiate between an infusion of the active compound and one of placebo. The only consistent complaint which was not also noted with placebo was constipation, first encountered at a dose of 80-μg/Kg. The incidence of headache was 15% for the granisetron group and 9% after administration of the placebo (Upward, 1990; Leigh, 1992).

2.3.2 Ondansetron - Ondansetron (trade name, Zofran. mfg. Glaxo) is also a 5-HT3 antagonist with a mechanism of action similar to granisetron, resulting in the inhibition of the nausea and vomiting reflex (Lip, 1990; Roberts, 1993; Scarantino, 1992; Tyers, 1989; Tyers, 1992). The acceptability of this drug for the treatment of radiation induced emesis is well documented in the literature (Kidgell, 1990; Henriksson, 1992; Priestman, 1989 et. al.). Ondansetron is available in

both oral and i.v. forms for use as an anti-emetic in cancer therapy. Ondansetron, an effective anti-emetic 5-HT3 antagonist, also produces minimal side effects, no dependence liability and no end organ toxicity (Smith, 1989). This drug is also well tolerated with no extrapyramidal reactions (Burnette, 1992). Ondansetron produces few side effects, the most common being headache and constipation (Burnette, 1992; Smith,1989). No major adverse events were reported after administration of ondansetron to 223 healthy volunteers or 438 psychiatric patients. Mainly two categories of symptoms, headache and constipation, appeared related to ondansetron, occurring more frequently in repeat compared to single dose studies. The incidence of headache following a single dose administration was 17% while constipation and abdominal discomfort has been reported to occur in 1% of the subjects (Seynaeve, 1991). In a placebo controlled study of healthy subjects, administered standard oral doses of either ondansetron (8 mg, 3 x daily) or granisetron (2 mg, once daily) over 13 days, results were equivocal with regard to cognitive and psychomotor performance decrements (Wetherell, 1994).

2.3.3 Prochlorperazine - Prochlorperazine (trade name, Compazine, mfg. SmithKline Beecham) was used as the positive control drug. Because the 5-HT3 antagonists have minimal or no side effects, prochlorperazine was selected from among other drugs used to treat radiation-induced emesis. Although primarily active at dopaminergic sites, prochlorperazine can influence 5-HT3 sites (Aapro, 1991; Dieras, 1990; Stewart, 1990). Conversely, 5-HT3 antagonists have been reported to indirectly influence dopamine sites (Costall, 1992; Minabe, 1992; Montgomery, 1993; Silverstone, 1992). Prochlorperazine is also used as a tranquilizer and anti-psychotic medication. This drug was anticipated to produce behavioral/cognitive effects at emesis inhibiting doses (Betts, 1991; Isah, 1991). Prochlorperazine can be administered orally and the rise time to peak plasma levels was considered acceptable for comparison with the target drugs.

Like the target anti-emetic drugs used in this study, prochlorperazine has been prescribed for the treatment of nausea induced by radiation and chemotherapy. Prochlorperazine is prescribed at dose levels as high as 40-mg, 3-4 t.i.d, therefore, the recommended 10-mg, single dose in this study was considered within safe parameters. This drug has known psychoactive properties such as drowsiness and dizziness. However, it was expected to present low risk for adverse reactions under conditions of a single dose administration. Extrapyramidal reactions can occur secondary to the administration of prochlorperazine. Tardive dyskinesia has been known to occur in patients treated with neuroleptics such as prochlorperazine. Although the prevalence of the syndrome appears to be highest among the very young and the elderly, it is impossible to rely on prevalence estimates to predict which patients are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and total cumulative dose of neuroleptic drugs administered to the patient increase (PDR, 1994). In a prospective study of the incidence of adverse events to prochlorperazine, there were 57 reported adverse reactions to prochlorperazine out of a patient population of 2,557. Sixteen of the 57 adverse events involved the extrapyramidal system. There were four dystonia-dyskinetic reactions, nine patients who developed Parkinsonian symptoms and three cases of akathisia. Of the patients who developed Parkinsonism, all but one were over the age of 60 yr. Among the 41 non-extrapyramidal adverse events, 6 were instances of sedation. The remaining reports were not obviously related causally to prochlorperazine (Bateman, 1988). Barbiturates or diphenhydramine are recommended for the treatment of extrapyramidal symptoms

(PDR, 1994). In the event of an extrapyramidal reaction, 50-mg of injectable diphenhydramine was available for administration by the study team physician.

In summary, the reasons for selecting prochlorperazine over other anti-emetic drugs were: (a) acceptable risk relative the incidence of adverse effects, (b) use in the treatment of severe emesis, (c) a mechanism of action related to the test drugs, (d) an acceptable serum-drug curve, and (e) prochlorperazine @ 10-mg p.o. was expected to impair performance on the cognitive test battery with subtle or very minimal side effects. Other classes of compounds used to treat emesis were considered to include: cholinergic antagonists (scopolamine), histamine antagonists (phenergan and diphenhydramine) and dopamine antagonists (metoclopramide, chlorpromazine and prochlorperazine). The dopamine antagonists were judged to be the best choice given their use in severe nausea and probable influence on 5-HT3 receptor sites. Among this class of drugs, prochlorperazine met the selection criteria better than the other compounds.

2.3.4 Drug Preparation - The target anti-emetic drugs, positive control drug and placebo were packaged in opaque capsules and identified as drugs a, b, c, and d to the investigators. The drugs and placebo tablets (placebo supplied by SmithKline Beecham) were cut using a pill cutter and loaded into the capsules by one of the investigators. Drugs were loaded independently, that is, only a single drug was on the table during pill cutting and loading of the capsules and the exact number of pills required were removed from the vial of pills provided by the drug company. At this point the drugs were identified by generic name, and, having been placed in individual containers, were provided to a person outside of the investigative team who served as a trusted agent for coding and blinding of test drugs.

2.4 Measures- Performance measures included a laboratory test battery, a complex air traffic control task, and a synthetic task representing the functions of a B-1B Defensive Systems Operator. Data were also collected to assess alterations in affective state and vigilance. Questionnaire techniques were used to establish sleep quality, fatigue levels and drug-induced symptoms. Physical, physiological and psychophysiological recording included: temperature, actigraphy, flicker fusion and serum-drug levels. See Data Collection Script, **Appendix A.**

2.4.1 Cognitive Performance - A Performance Assessment Battery (PAB), selected from the UTC-PAB/AGARD STRES Battery (Reeves, 1991; Schlegel, 1992), was self administered at recurring hourly intervals using a workstation computer. The PAB contained five widely used performance tests designed to detect changes in thinking, reasoning, memory, decision making and motor abilities. The tests were chosen based on presumed sensitivity to the effects of drugs and environmental stressors. The five tests in order of presentation were: Matrix Rotation, Continuous Recognition, Manikin / Mathematical Processing (attention switching), Grammatical Reasoning and Unstable Tracking. For test descriptions, see Performance Assessment Battery, **Appendix B.** The PAB required approximately 15 min to complete and was administered for baseline data collection and at the beginning of each hour during the drug treatment / test period of approximately 8 h.

2.4.2 DSO Analog - A Synthetic Task - A complex, multi-dimensional synthetic task was presented immediately following each PAB. This task, referred to as the Analog, symbolically

represents the task functions of a B-1B Defensive Systems Officer to detect, identify and defend against a variety of threats in the operational environment (Trafton, 1995). The Analog is a complex, composite test of pattern recognition, tracking, memory, strategy optimization and decision making. Twelve threats were presented in random sequence for a total of 36 threat presentations during each Analog test which required approximately 12 min. The Analog was developed to demonstrate a complex synthetic task and is based on a task analysis and decomposition of a B-1B Defensive Systems Officer station and functions. For additional details see Instructions for the DSO Synthetic Task, **Appendix C**.

2.4.3 Vigilance - Following the Analog, a Vigilance test was administered taking approximately two min. Subjects were presented with a "target" of concentric rings and were challenged to monitor a pattern of dots to determine if there were more that one dot in any ring on a given stimulus presentation. For two dots in a single concentric ring, the required response was the "S" key for Signal. If only one dot was present in each concentric ring the required response was "N" for Noise. Patterns were changed quasi-randomly (i.e. not immediately following the subject's response) and therefore the test demanded continuous attention on the part of the subject. This test was also repeated during each hour of testing, in addition to the collection of baseline scores.

2.4.4 Profile of Mood States - During hours 1, 2, 3, and 7 (just prior to blood draws), affective state and vigor were assessed using the Profile of Mood States (McNair, 1971) and the Visual Analog Scale (Monk, 1989). Prior to the start of the experiment, baseline scores were collected using both assessment tools. POMS is a 65 item, six dimension mood scale representing various affective states. Subjects respond to adjectives which represent the six mood states. The six dimensions are: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Confusion-Bewilderment and Fatigue-Inertia. Responses to the adjectives are based on a 5 point scale ranging from "extremely" to "not at all".

2.4.5 Visual Analog Scale: Affective State and Vigor - A computer based Visual Analog Scale was also used to detect changes in mood and level of activation. Subjects are presented with a question, below which appears a horizontal line representing an analog scale. Labels at either end of the line indicate opposite extremes of mood or vigor. The subject selects a point along the analog scale by moving a cursor with the right or left arrow keys and pressing return to enter the response. The location of the cursor represents the subject's mood state between the two extremes. This assessment is based on eight unipolar visual analog ratings, four primarily concerned with subjective activation or vigor (alertness, sleepiness, effort and weariness) and four concerned with feelings of affective state (happiness, sadness, calmness and tension) (Monk, 1989).

2.4.6 Symptoms Questionnaire - Also administered during baseline data collection and during hours 1,2,3 and 7 was a Drug Symptoms and Side Effects Questionnaire. The checklist provided a list of 26 common physical symptoms and subjects were asked to check a block if they were experiencing a symptom and to indicate symptom severity on a scale of one to seven, with one being described as slight and seven described as severe. Subjects were also asked to assess the cause of any reported symptoms and to rate the extent to which the symptom would impair their ability to perform normally assigned military tasks to include driving to and from work.

A physician's assessment of the cause was completed at end of the study when symptoms and blood assay data could be reviewed in the context of the drug treatment condition. See Test Symptoms Checklist, **Appendix D.**

2.4.7 Fatigue Scale - The USAF School of Aerospace Medicine (SAM) Subjective Fatigue Scale was administered for baseline testing and every hour during the experiment (Boll, 1993). The scale asks the subject to select the number corresponding to a statement which best describes "how you feel right now". There are seven statements ranging from statement #1, "fully alert", to statement #7, "completely exhausted". The subjective fatigue score together with sleep hours and a quality of sleep rating were recorded on an activity log. See Activity Log provided at **Appendix E.**

2.4.8 Actigraph Recording - Subjects wore wrist style activity monitors to provide an independent record of sleep periods and quality of sleep (Elsmore, 1993). Subjects wore the actigraphs continuously beginning one day before testing and ending one day following the completion of the last test session.

2.4.9 Temperature Recording - Oral temperatures were self measured using the Becton-Dickinson thermometer, model 2860. These digital thermometers are sensitive to 0.1 ^{0}F and produce audible and visual indications when a stable temperature is reached. During testing, subjects were not allowed to eat or drink anything for at least 15 min prior to taking their oral temperature. Subjects recorded their temperatures hourly on the Activity Log, **Appendix E.**

2.4.10 Blood - During hours 1,2,3 and 7, a 10-cc blood sample was drawn from each subject by the team physician. Blood samples were usually drawn via a heparin lock, venous catheter implanted by the research team physician. In a small number of cases, due to catheter failure, individual needle sticks were used to obtain blood samples. Blood samples were allowed to coagulate for approximately 20 min and separation of serum from whole blood products was accomplished by centrifugation. Prochlorperazine was extracted from serum by the liquid-liquid method while granisetron and ondansetron were extracted by 10-ml. to 100-ml. Varian C2 columns. Prochlorperazine and granisetron were chromatographed with a Spherisorb CN column and detected by electrochemistry. Ondansetron was separated by a C18 column and detected by UV spectroscopy.

2.4.11 Complex Performance Task - During baseline data collection and hours 4, 5 and 6 (hours when there were no blood draws), TRACON (Terminal Radar Approach Control, Wesson Corp., Austin, TX), a terminal radar approach and control simulation was used to collect performance scores. Subjects did not receive training on this task prior to the experimental trials as they did with the other performance tests. TRACON was used to keep subjects alert and to place continuous task demand on the subjects during the experimental sessions. TRACON is a complex task and provided a limited opportunity to assess the effects of drugs and fatigue on original learning. This Personal Computer (PC) based simulation displays a radarscope at a large metropolitan airport. With an automated flight strip display and communications panel, the subject acting as an air traffic controller must handle all the aircraft in the sector. The number of

planes, their type, altitude, airspeed, and direction can be controlled for continuous simulations. The quality of the weather and the pilots response to the controller can also be varied. The number of aircraft successfully landed, the number of missed approaches and the average time to landing are all recorded at the end as the subject/controller score. Also recorded are the number of near calamities such as separation conflicts and other mid-air near misses or incidents. TRACON is made for the PC and runs on a variety of preselected simulations.

2.4.12 Flicker Fusion - The Critical Flicker Fusion (CFF) threshold for each subject was measured and recorded during baseline data collection and at the end of each hour of testing (except for hour #8). CFF appears to be affected by a variety of conditions which affect the functional efficiency of the cerebral cortex and has been used in a number of studies investigating psychotropic drugs and fatigue (Smith, 1976). Subjects were tested individually by peering into a viewer with both eyes and adjusting the flicker frequency from two stationary light sources (two red bars) until the sensation of flicker disappeared and the light became steady.

2.5 Training and Test Facilities - Training and testing were conducted in a trailer which had been specially designed and constructed as a restricted access, test bed for MX mobile rail garrison missile launch crews. The trailer inside dimensions are approximately 55 ft long x 9 ft wide x 10 ft high, There are no windows and lighting was provided by florescent light fixtures controlled by a rheostat. During testing, the light levels were adjusted downward to approximately 200-lux to minimize glare from the CRT screens. Temperature was maintained within a comfortable range of approximately 72 - 75 degrees. In the test area of the trailer, the walls are covered with carpeting for sound attenuation. The trailer contains a functional bathroom, kitchen and bunk areas. The launch control area in the rear of the trailer was modified for blood collection and preparation of blood serum. Each subject was provided an individual workstation consisting of a 30w x 24d x 28h table, adjustable office chair and Pentium, 90-MHz PC equipped with Microsoft compatible mouse. Workstations were setup, lengthwise, in two rows of four workstations adjacent to each longitudinal, outside wall. Cloth covered, moveable dividers, placed to the front and rear, created a cubical open to the center aisle. The two rows of workstations were offset and divided by the center aisle providing investigator access to the subjects. Therefore, subjects were not in total isolation from one another or from the investigators.

2.6 Training and Test Procedures - Subjects were trained on the performance test battery during the week preceding the experimental trials. Subjects reported at 1630 h for two hours of training on consecutive days (Tuesday through Friday); immediately preceding the drug test trials. Each subject received 4 exposures to the performance test battery per day for a total of 16 pretrial exposures. Previous experience with this specific test battery in a study of B-1B crews flying prolonged, back-to-back missions has demonstrated acceptable stability in subject performance by the 16th training session (French, 1995). Subjects also received 15 pre-test training trials on the synthetic analog task and three pre-exposure training trials to the vigilance task. Testing began the day immediately following the last training day.

For logistics reasons (i.e. not for the purpose of experimental design), the 24 subjects were divided into 3 groups with each group being tested over an 8 day period. Within a group,

subjects were tested every other day (48 h between treatment conditions) to allow for drug washout. Testing 8 subjects in each group was the maximum that could be accommodated in the performance laboratory and permitted 2 subjects to be tested under each of the 4 treatment conditions on any single day of the experimental trials. Drug order was randomly assigned and the order groups were in conformance with a 4 x 4 Latin Square design.

Subjects were asked to remain awake during the morning and afternoon hours preceding the test sessions which began at 1630 h. Because the first day of testing was on a Saturday, this requirement was established by verbal agreement with the subject. On subsequent test days, subjects were required to work a full duty day, reporting to the performance laboratory after work at 1630 h. When the washout day (the day following a drug test session) was a duty day, subjects were required to take annual leave for the purpose of fatigue recovery.

On test days, subjects arrived at the performance laboratory between 1630 h and 1640 h. Each subject was provided a script which detailed test preparation activities and the planned data collection timelines. See Data Collection Script, **Appendix A**. During the first hour indwelling venous catheters were inserted, an Activity Log documenting sleep hours and quality of sleep ratings during the preceding night was filled out, and on test days 2, 3, 4 and post-test day 6, subjects completed a Delayed Symptoms Checklist identical to the symptoms checklist at **Appendix C**. Following catheter insertions, subjects practiced TRACON (described under section 2.4.11) and completed a 10 minute test to establish a TRACON baseline score. Between approximately 1730 and 1845 h., subjects established baseline scores for the Performance Assessment Battery, the B-1B Defensive Systems Analog, the Vigilance test, the Profile of Mood States, the Visual Analogue Scale (affective state and vigor) and, a baseline Symptoms checklist. Subjective Fatigue scores and oral temperatures were entered on the Activity Log. Each subject received a baseline Critical Flicker Fusion test. After a 10 minute restroom break, subjects returned to their workstations and remained seated while the study team physician and one of the principle investigators distributed the treatment drugs. This was done only after referring to a table showing the prescribed subject x day x drug treatment code, together with confirmation of the correct drug selection by a second investigator.

Subjects swallowed their capsules at 1900 h and immediately proceeded to the Performance Assessment Battery, Defensive Systems Analogue task, Vigilance test, POMS, SACS, Symptoms checklist, Subjective Fatigue scale and temperature measurement. At approximately 40 min past the hour, 10-cc of blood was drawn from each subject followed by each subject being given a Critical Flicker Fusion test. This same sequence of events was repeated for the first three hours and at hour 7. During hours 4, 5, 6 and 8, blood was not drawn and the subjects did not take POMS, SACS or complete a Symptoms checklist. During these periods, performance scores were collected using the PAB, the Synthetic Analog the Vigilance test and TRACON. Subjective Fatigue, oral temperature scores were also collected during hours 4, 5, 6, and 8. Critical Flicker Fusion testing was also administered during each of these periods except for hour #8. Testing was completed at 0230 hours.

In regard to miscellaneous aspects of the testing, subjects were encouraged to wear comfortable attire and were not permitted to consume food or drink other than water and a snack of one fruit

cup (4.4-oz), one pudding cup (4.4-oz) and one 6-oz can of orange juice provided each test night at 2333 h. Social interactions were kept to a minimum due to near continuous test activity. Subjects were encouraged to remain alert and sleeping was not permitted at any time. Except for use of a nearby restroom, subjects were not permitted to leave the test area. At the completion of each experimental session subjects were transported to quarters by a qualified driver who was not a subject participant in this study. Three investigators were present during each of the test sessions.

3.0 RESULTS

3.1 Data Analysis - For all tests and questionnaires, the first data point represents a baseline trial followed by drug administration at 1900 h. All results are discrete vs. continuous data and were collected during recurring intervals beginning at the approximate clock times indicated on the graphs. For exact times of test administration, see **Appendix A**, Data Collection Script. All data points reflect treatment group means. Data for all performance tests were analyzed using a four way ANOVA technique. Main effects and interaction effects were evaluated for: drugs, trials, drug orders, and test sessions (days). Throughput results are based on a rate per minute interval and are calculated as: $60{,}000_{ms}$ / Reaction $Time_{ms}$ x Proportion Correct. A three way ANOVA (drugs, trials, and drug orders) was run on the fatigue, critical flicker fusion and temperature data because learning effects were considered unlikely. Mood and vigilance data were analyzed using a nonparametric test developed by Connover of Texas Tech University. This technique is an extension of Friedman's Multi-Sample Test. Data were analyzed using SAS procedures. SAS is a registered product of SAS Institute, Inc. Cary, NC.

3.2 Cognitive Performance Tests - The target anti-emetic drugs, granisetron and ondansetron, produced no statistically significant effects on cognitive or psychomotor performance. On the Performance Assessment Battery (PAB), two of the five tests (Attention Switching and Unstable tracking) resulted in statistically significant drug by-trial interactions for some but not all of the principle variables of interest i.e. accuracy, reaction times, and throughput. However, these results seem to reflect the diminished performance attributable to a fairly consistent positive control (prochlorperazine) induced performance decrement. This drop in performance typically began between hours four and five, post drug administration, and remained evident through the completion of a test session, although there was frequently some recovery on the final trial probably due to diminished serum-drug levels or changes in subject motivation. These results are in reasonably good agreement with the serum-drug curves for this group of subjects. All of the performance tests produced a highly significant by-trial (fatigue) effect consistent with expectations regarding subjects who typically had worked a full eight hour shift preceding the beginning of the experimental trials and concluding at 0230 hours - nine hours from the start of subject instrumentation and baseline data collection. Except for Unstable Tracking, there were statistically significant learning effects present in the comparisons across test sessions for the other performance battery tests.

3.2.1 Attention Switching - The *Attention Switching* task produced the most consistent pattern of results, providing evidence of modest performance improvement over the first two to four trials, followed by a relative decline suggesting a fatigue effect. This usually became evident at

about trial four and continued through the end of the test session. On the Attention Switching-Manikin part of the test, there was a significant by-trial effect (p<.0001) for each of the three main variables of interest: accuracy, reaction time, and throughput. There were also significant drug-by-trial interaction effects for these same variables (p<.05, p<.01 and p<.0005), **Figures 3.2.1-1, 2 ,& 3.**

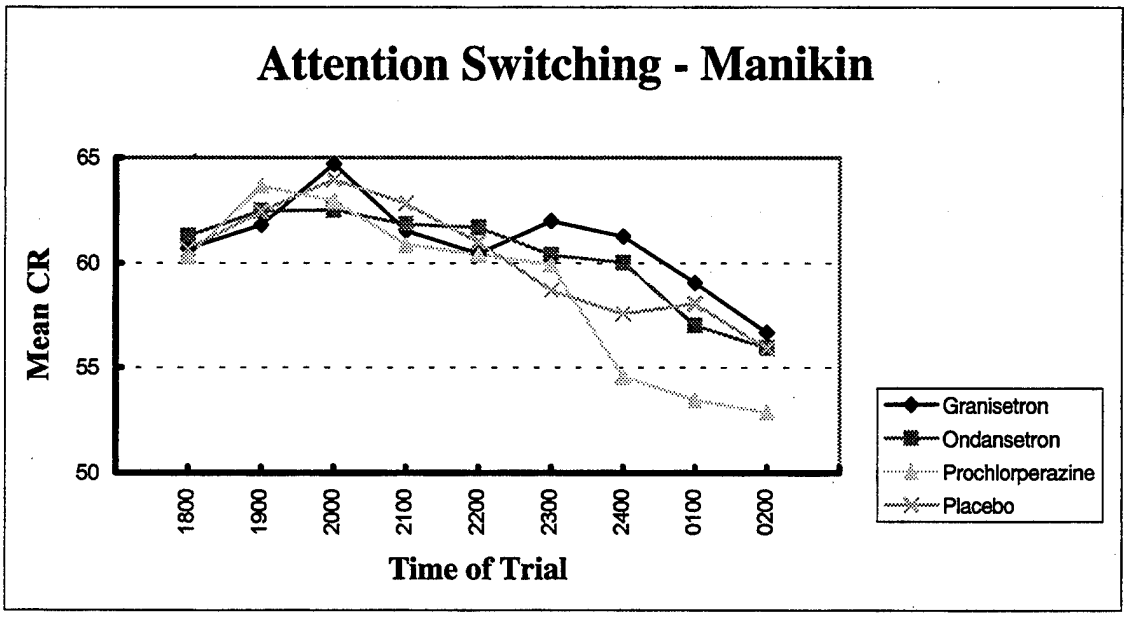

Figure 3.2.1-1: Manikin Correct Response (CR)
Trial = p < .0001
Drug x Trial = p < .05

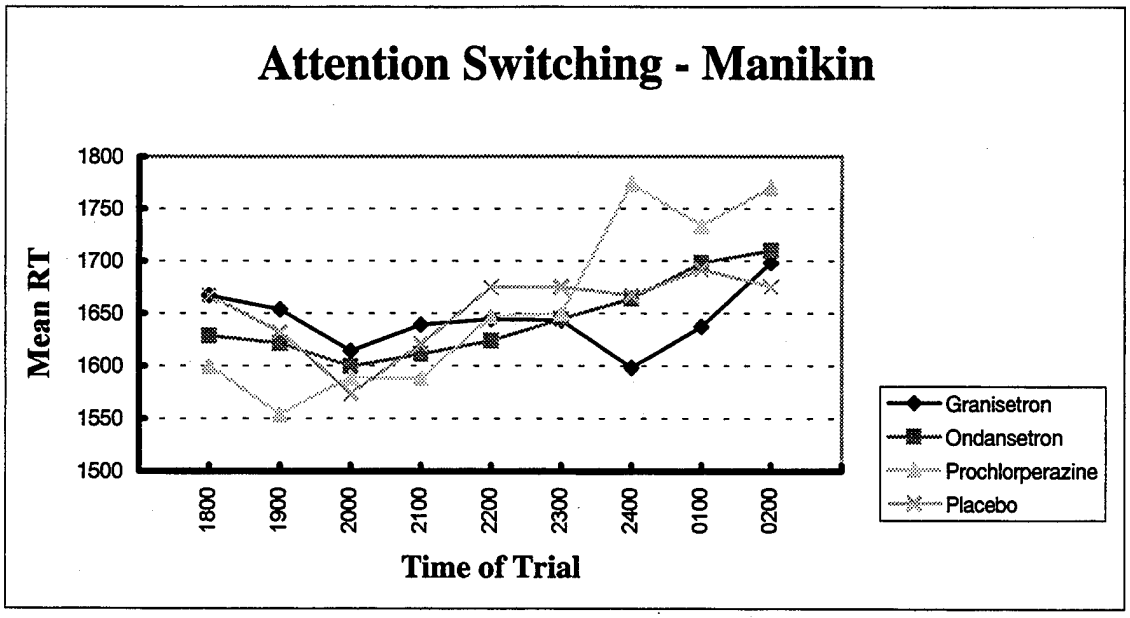

Figure 3.2.1-2: Manikin Reaction Time (RTmsec), correct trials
Trial = p < .0001
Drug x Trial = p < .01

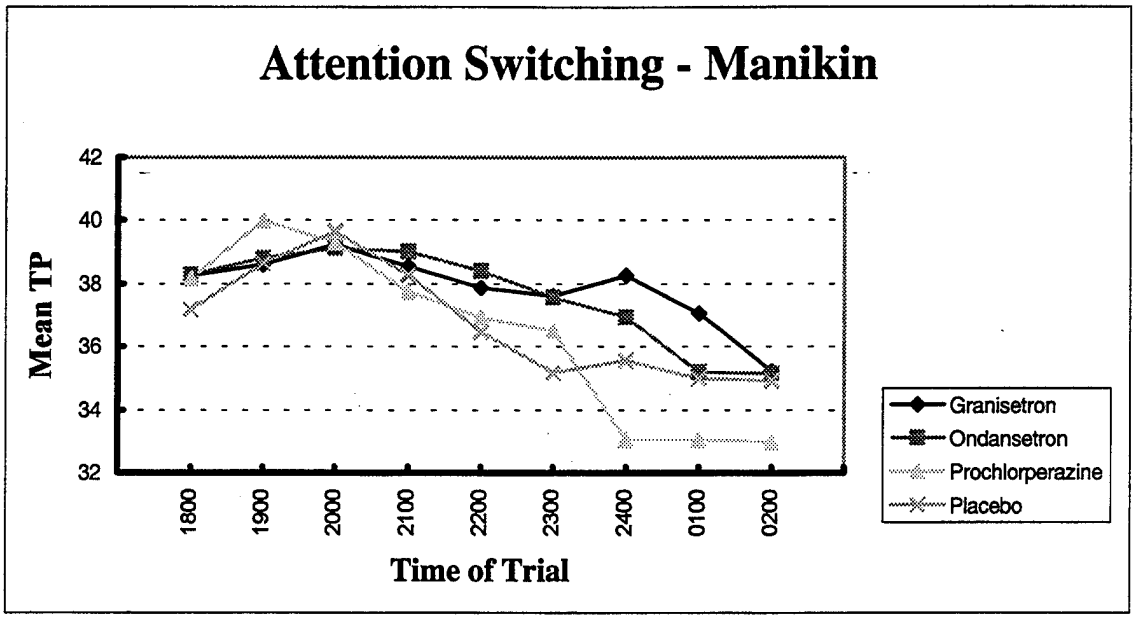

Figure 3.2.1-3: Manikin Throughput (TP)
Trial = p < .0001
Drug x Trial = p < .0005

An identical analysis of the Attention Switching-Math part of the test, produced similar results with statistical significance equaling or exceeding the p<.0001 level for trials on each of the three dependent variables. Only the accuracy variable showed a drug-by-trial effect (p<.05), **Figures 3.2.1-4, 5, & 6.**

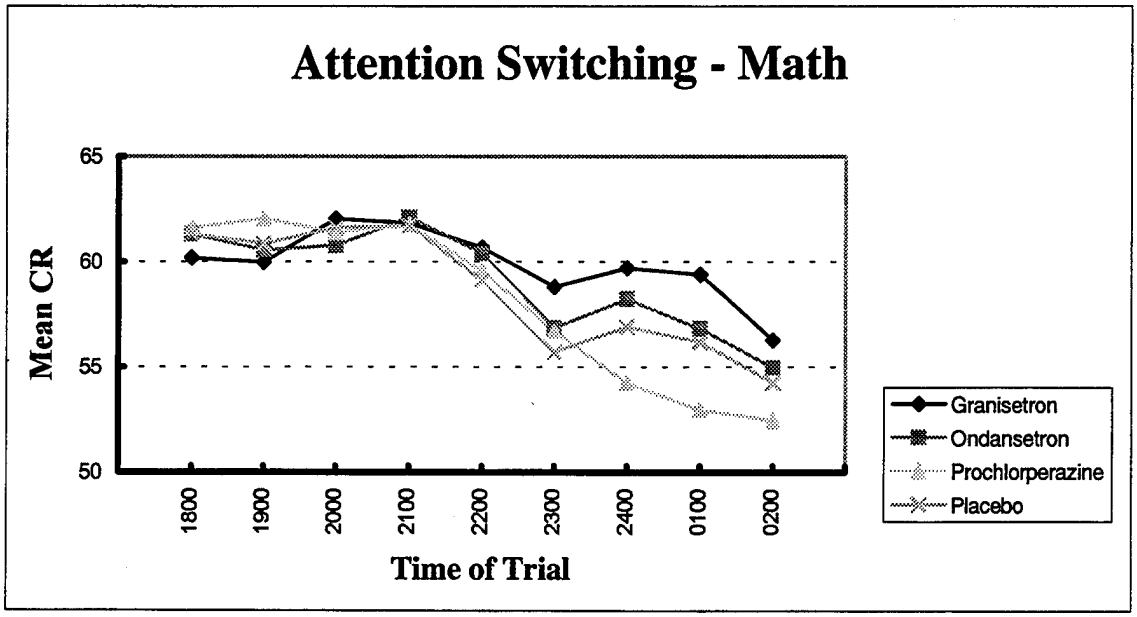

Figure 3.2.1-4: Math Processing Correct Response (CR)
Trial = p < .0001
Drug x Trial = p< .05

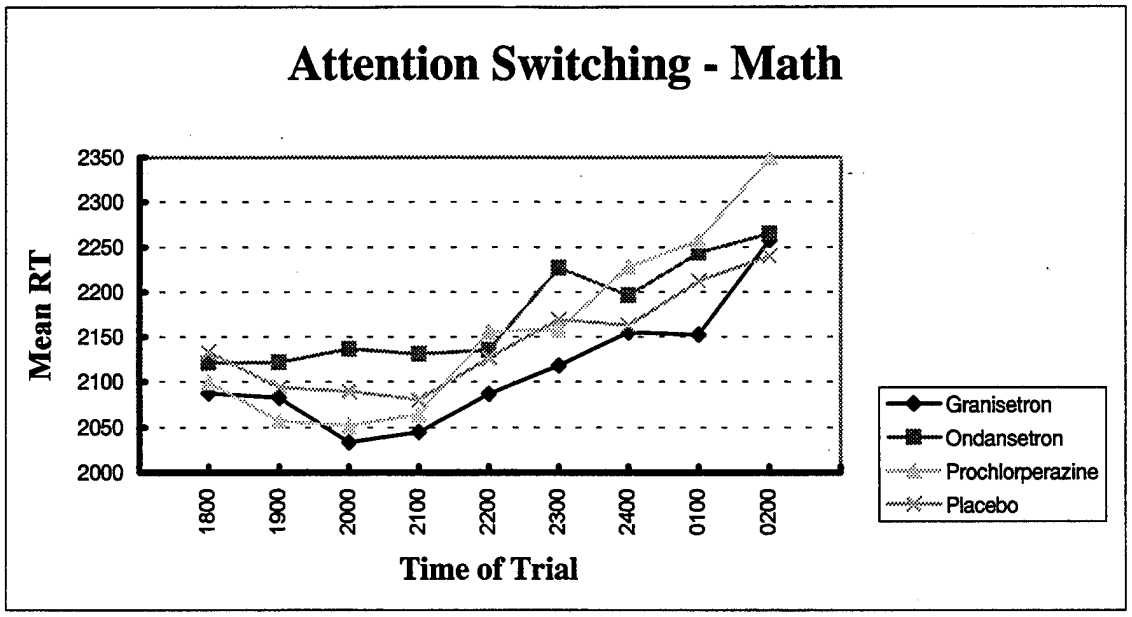

Figure 3.2.1-5: Math Processing Reaction Time (RTmsec), correct trials
Trial = $p < .0001$

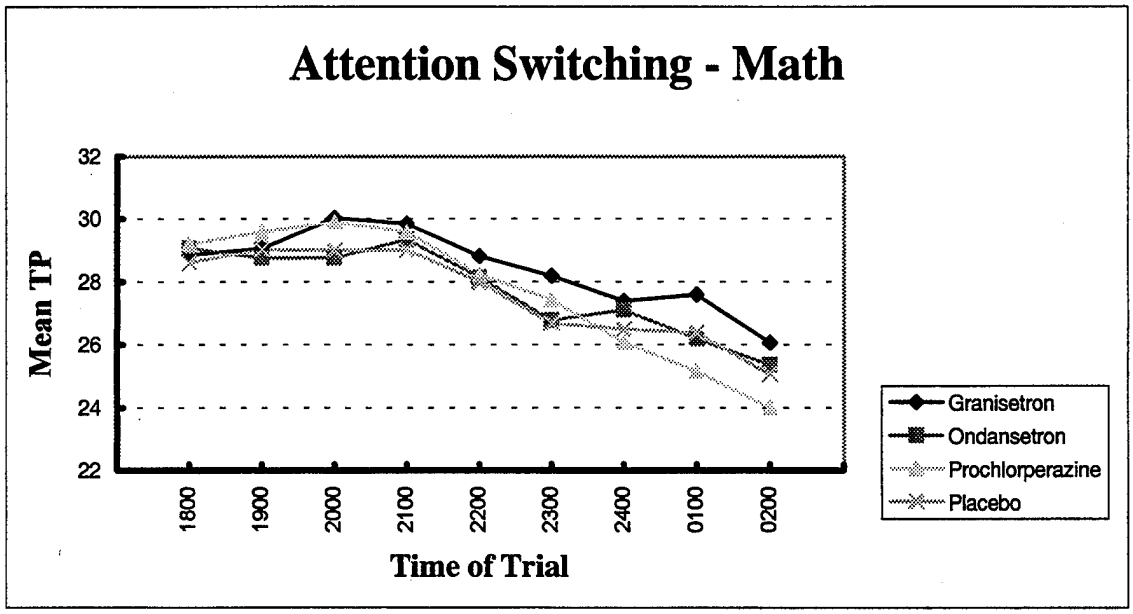

Figure 3.2.1-6: Math Processing Throughput (TP)
Trial = $p < .0001$

Subsets of these data were reviewed for accuracy and reaction times during trials when the subject had to switch from one task e.g. math to the other task e.g. manikin. These results reflect a decline in overall performance as would be expected, but nevertheless confirm similar fatigue trends and positive control drug effects. As with the primary Attention Switching test results, these data subsets demonstrate no differences between the target drugs, a strong fatigue effect and consistent positive control effect beginning about four hours into the experimental trials, **Figures 3.2.1-7, 8, 9, & 10.**

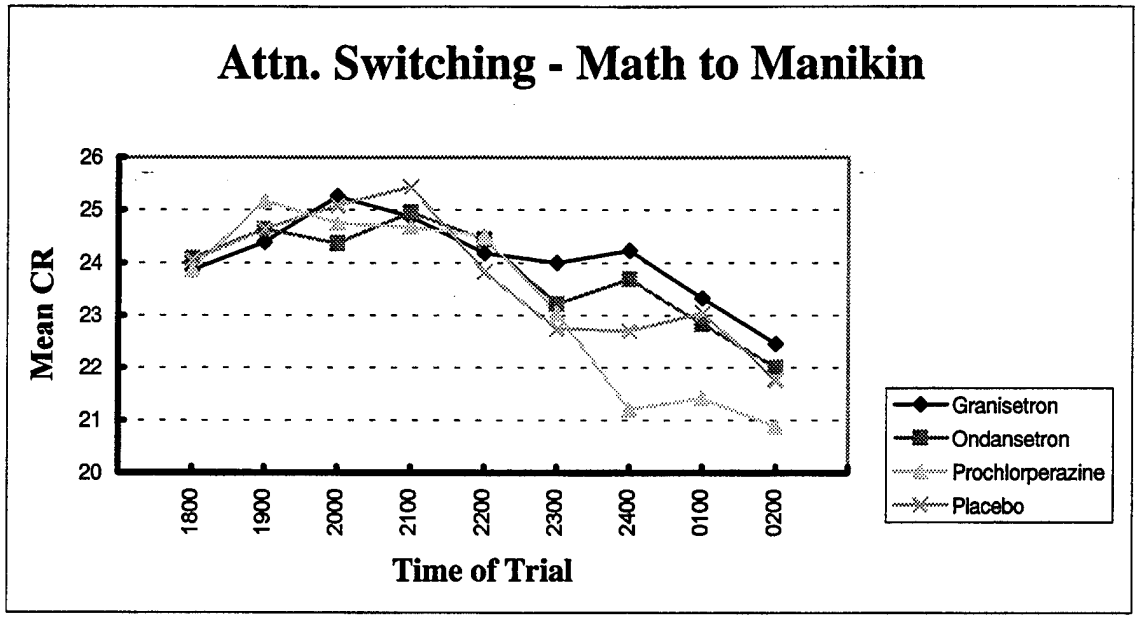

Figure 3.2.1-7: Math to Manikin Correct Response (CR)
Trial = p < .0001
Drug x Trial = p < .01

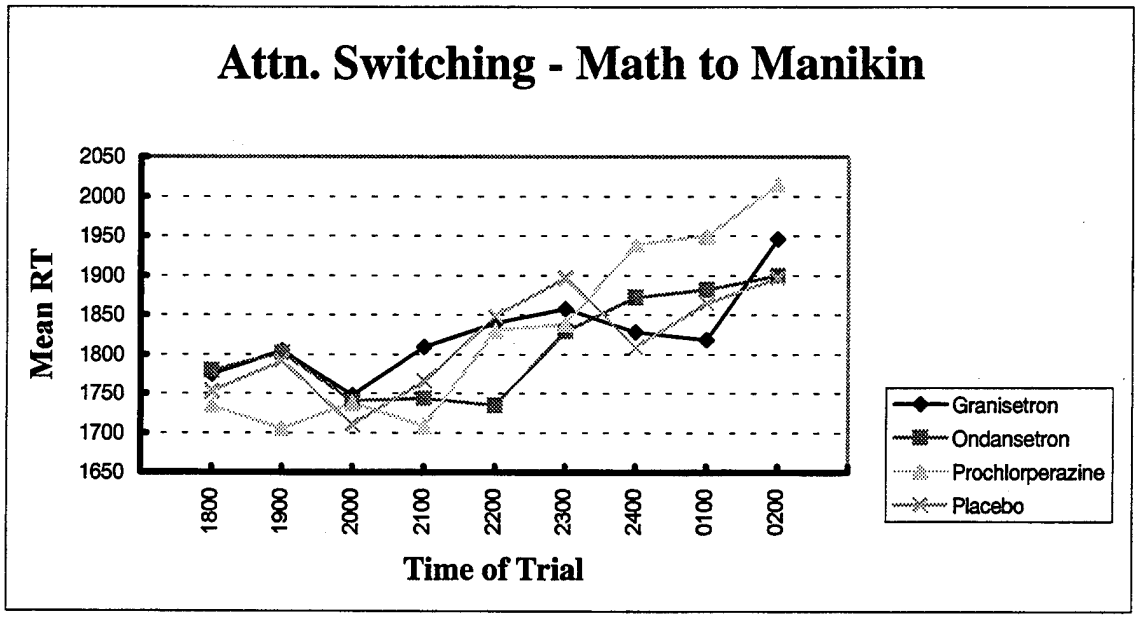

Figure 3.2.1-8: Math to Manikin Reaction Time (RTmsec), correct trials
Trial = p < .0001

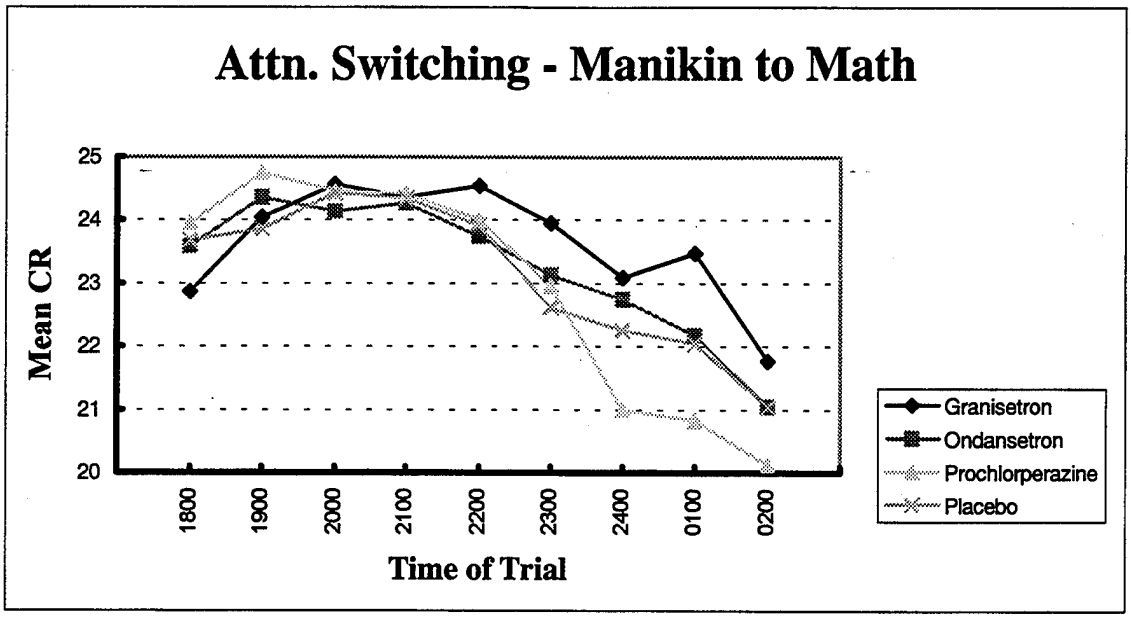

Figure 3.2.1-9: Manikin to Math Correct Response (CR)
Trial = p < .0001
Drug x Trial = p < .05

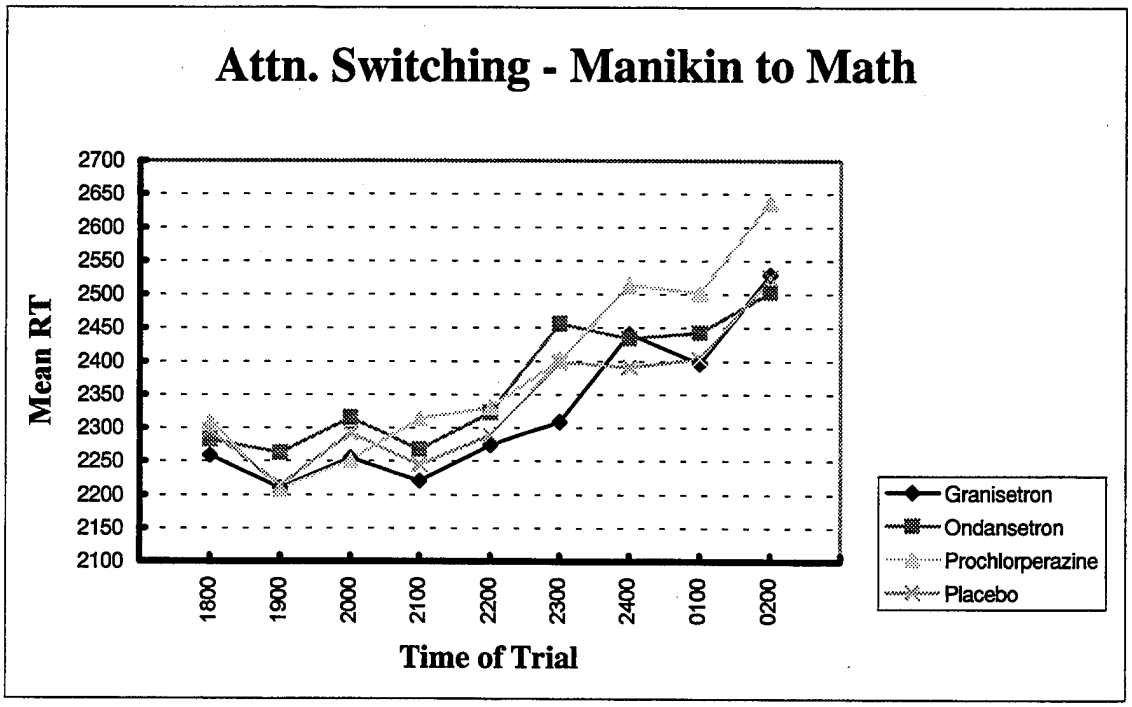

Figure 3.2.1-10: Manikin to Math Reaction Time (RTmsec), correct trials
Trial = p < .0001

3.2.2 Unstable Tracking - The *Unstable Tracking* test was similarly sensitive to the effects of fatigue and the positive control drug. There were no target drug effects. The variables of interest were: maximum lambda, mean lambda, RMS. error, and the number of control losses. A variable difficulty level (lambda) was used to displace a cursor which the subject was required to

manipulate, using mouse input. Control losses were counted whenever the cursor disappeared from either side of the computer screen as a result of the subject's inability to command the cursor position at or near to the center of the computer screen. Performance on this test typically remained level through trial four or five, followed by a steady decline through trial eight which preceded the final run of the PAB for each test session. On this final trial there was sometimes a slight performance improvement typical of that observed in previous studies and most likely attributable to an increase in motivation associated with reaching the end of an arduous experimental regimen. Trial effects were statistically significant for the variables mean lambda ($p<.0001$), maximum lambda ($p<.0001$), and control losses ($p<.0001$). There was also a significant drug-by-trial interaction effect ($p<.05$) for the number of control losses. The only statistically significant drug main effect, among all of the PAB tests, occurred in the number of control losses on the Unstable Tracking task ($p<.01$). This outcome is most likely attributable to diminished performance caused by the prochlorperazine condition. All plots reflect means by trial for each treatment condition, **Figures 3.2.2-1, 2, & 3.**

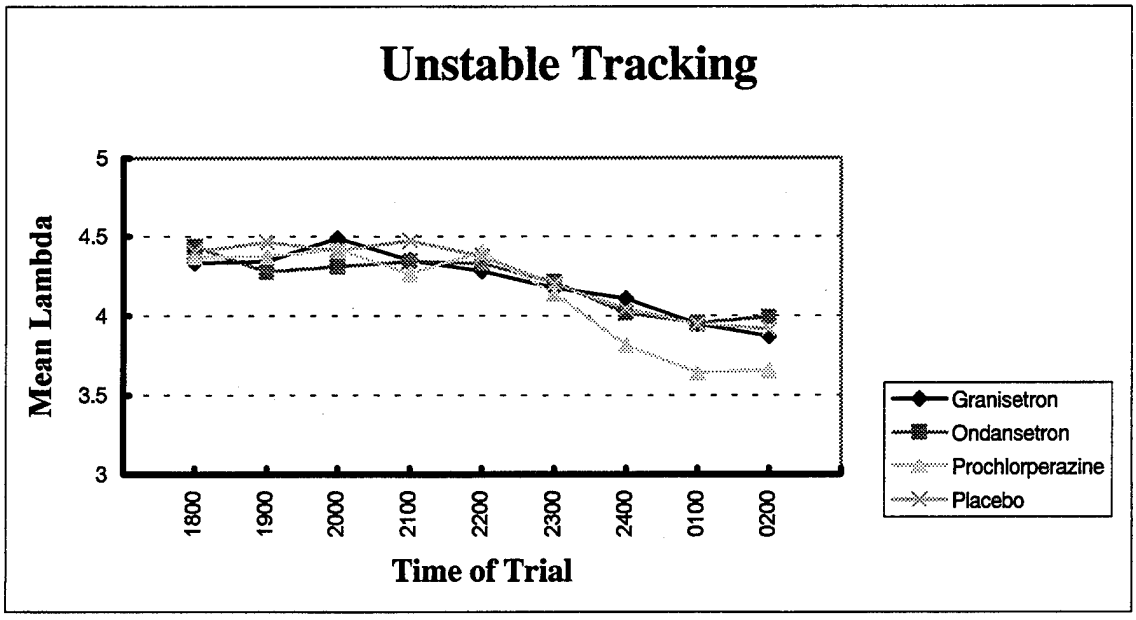

Figure 3.2.2-1: Unstable Tracking Mean Lambda
Trial = $p < .0001$

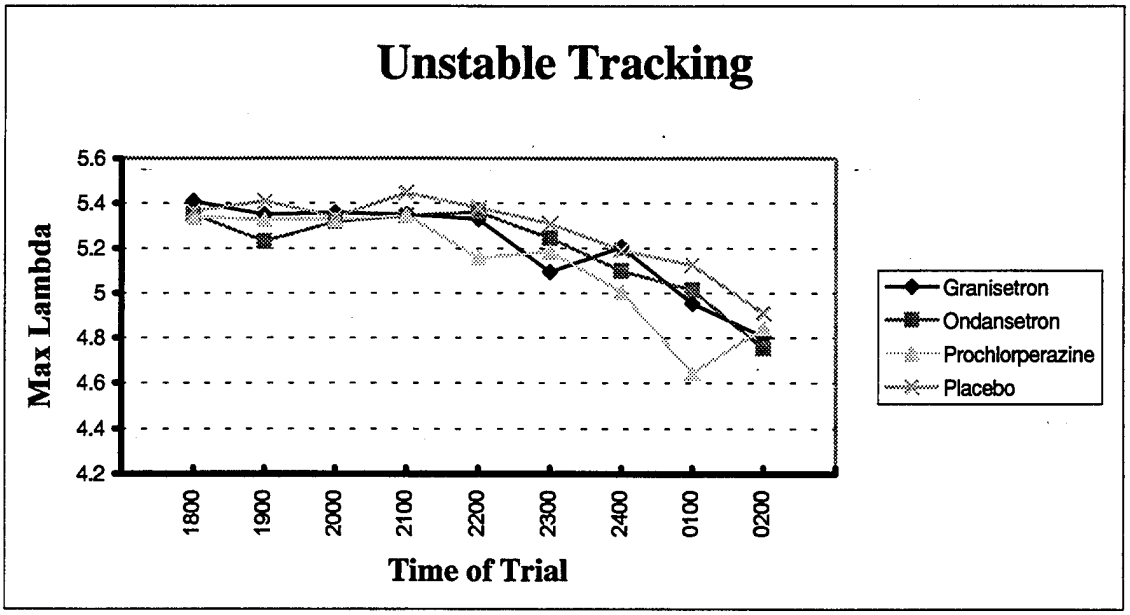

Figure 3.2.2-2: Unstable Tracking Maximum Lambda
Trial = $p < .0001$

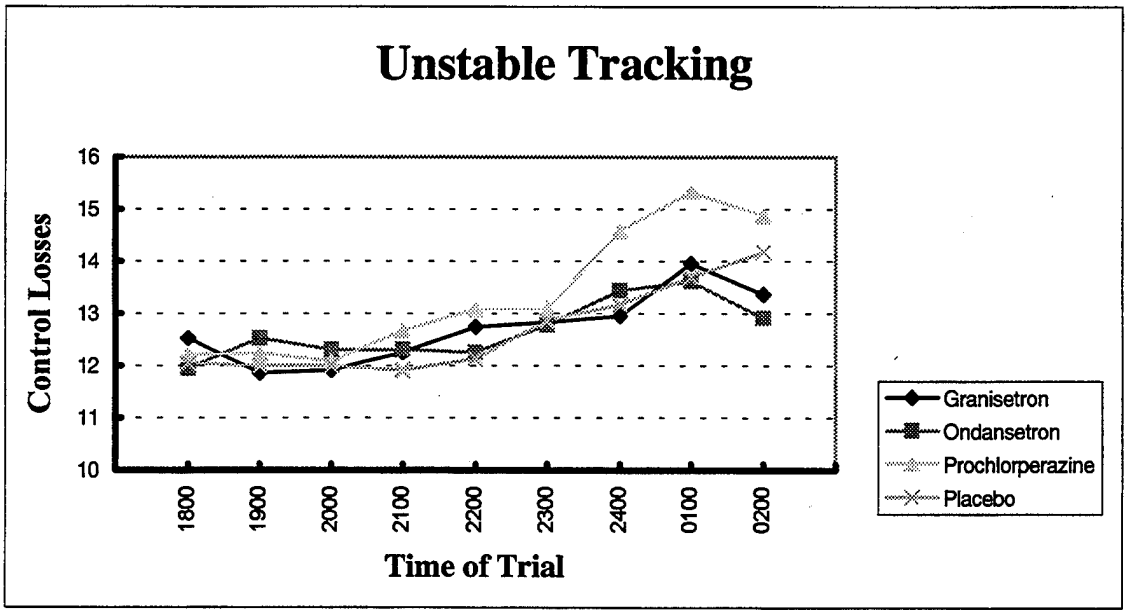

Figure 3.2.2-3: Unstable Tracking Control Losses
Trial = $p < .0001$
Drug = $p < .001$
Drug x Trial = $p < .05$

RMS error scores were highly variable and without statistical significance or obvious trends, **Figure 3.2.2-4.**

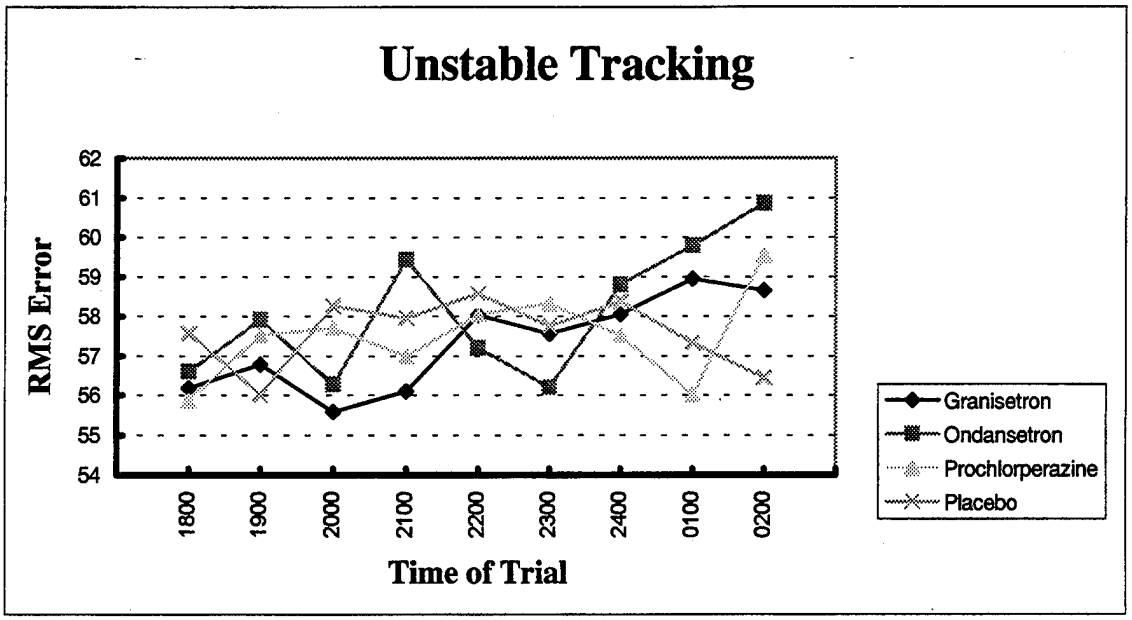

Figure 3.2.2-4: Unstable Tracking RMS Error n/s

3.2.3 Matrix Rotation - Results from the *Matrix Rotation* task were inconsistent with no drug main effects. There were statistically significant by-trial effects for accuracy ($p<.0005$) and throughput ($p<.0001$). As can be observed form the graphic representation of the means data for accuracy, there was a very minimal decrease in performance over trials. Reaction times are variable and with mixed results by drug treatment condition. The graph depicting throughput also suggests only slightly decremented performance over trials. These data are interpreted to reflect tightly banded within subject variability which is influenced to only a minor extent by the time course of trials and associated fatigue. This apparent lack of sensitivity for this test was not especially surprising since the Matrix Rotation task, at least intuitively, seems to place minimal cognitive demand on the subject after a high level of task learning has been achieved, **Figures 3.2.3-1, 2, & 3.**

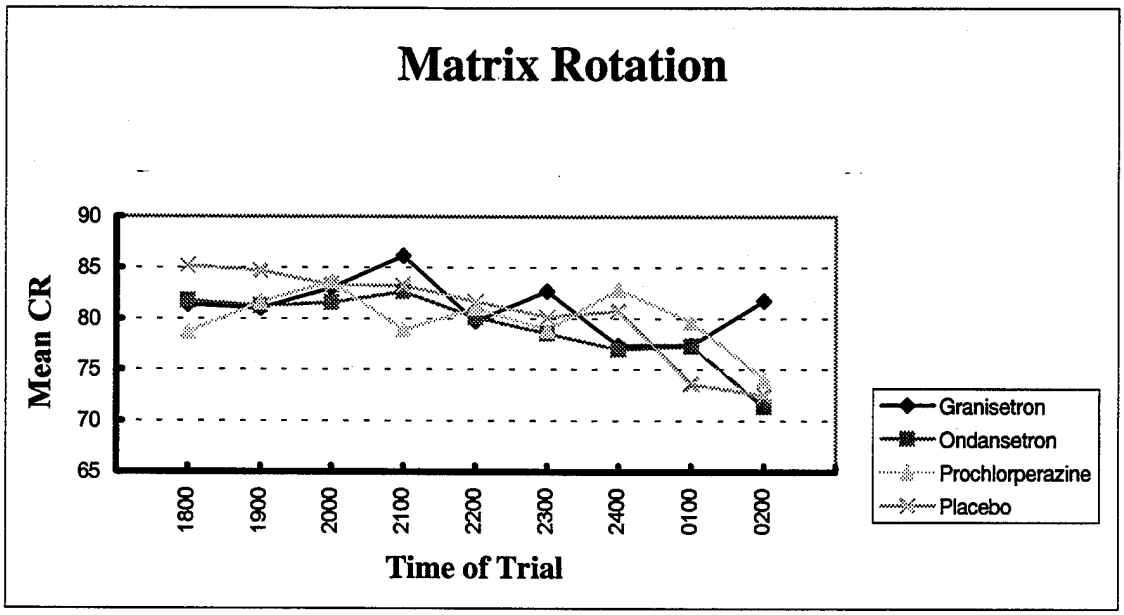

Figure 3.2.3-1: Matrix Correct Response (CR)
Trial = $p < .0005$

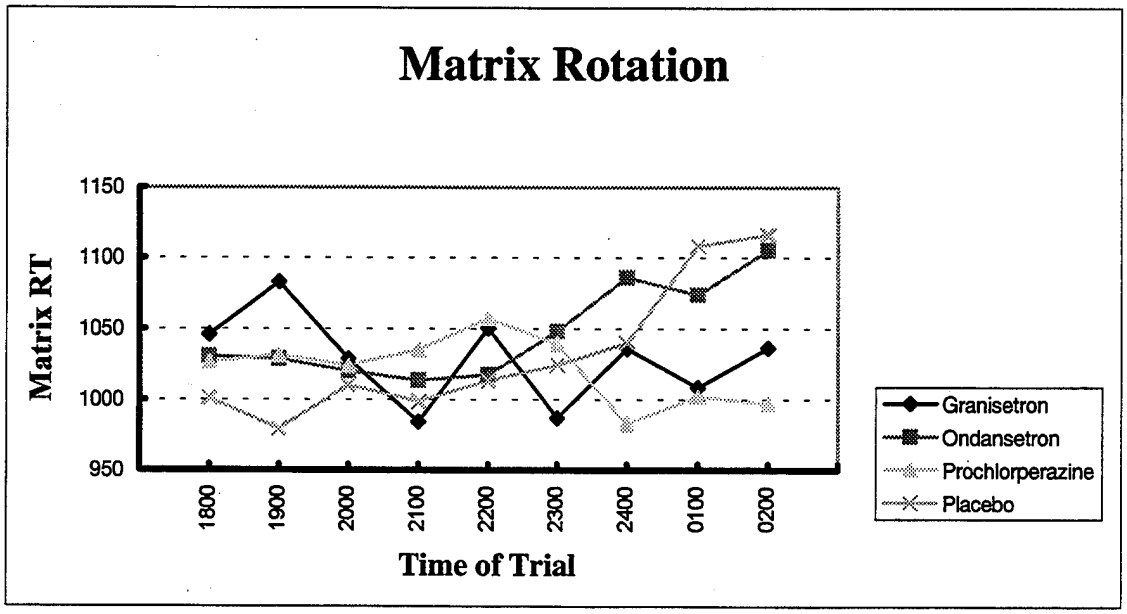

Figure 3.2.3-2: Matrix Reaction Time (RTmsec), correct trials
n/s

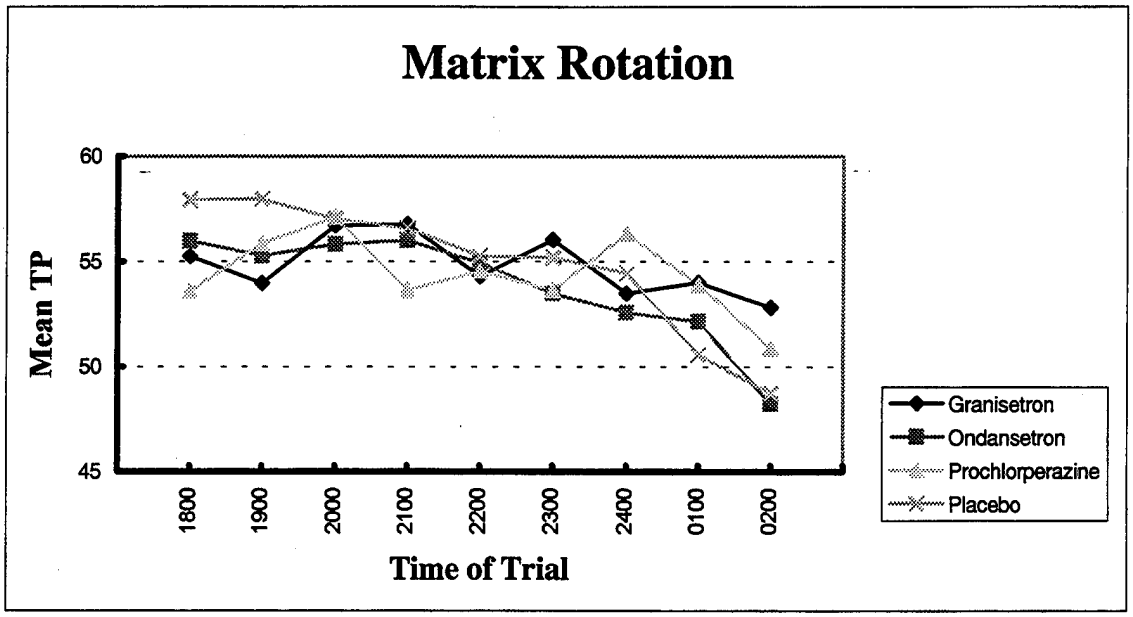

Figure 3.2.3-3: Matrix Throughput (TP)
Trial = p < .0001

3.2.4 Continuous Recognition - Data from the *Continuous Recognition* test showed trends more similar to the Attention Switching test, although the effect of the positive control drug was considerably less dramatic, or for the most part, absent across trials. The data for the three main variables of interest (accuracy, reaction time and throughput) demonstrate a rise in performance over the first three trials, presumably a warm up effect, followed by a relatively continuous diminution in performance over the remaining trials. During the later trials, there appears to be a slight positive control effect (although nonsignificant) beginning at trial five and continuing with the exception of trial eight to the end of the test session. There were no target drug effects revealed by the statistical analysis. Trial effects were again highly significant for accuracy ($p<.0001$), reaction time ($p<.001$), and throughput ($p<.0001$), demonstrating the sensitivity of this test to fatigue, **Figures 3.2.4-1, 2, & 3.**

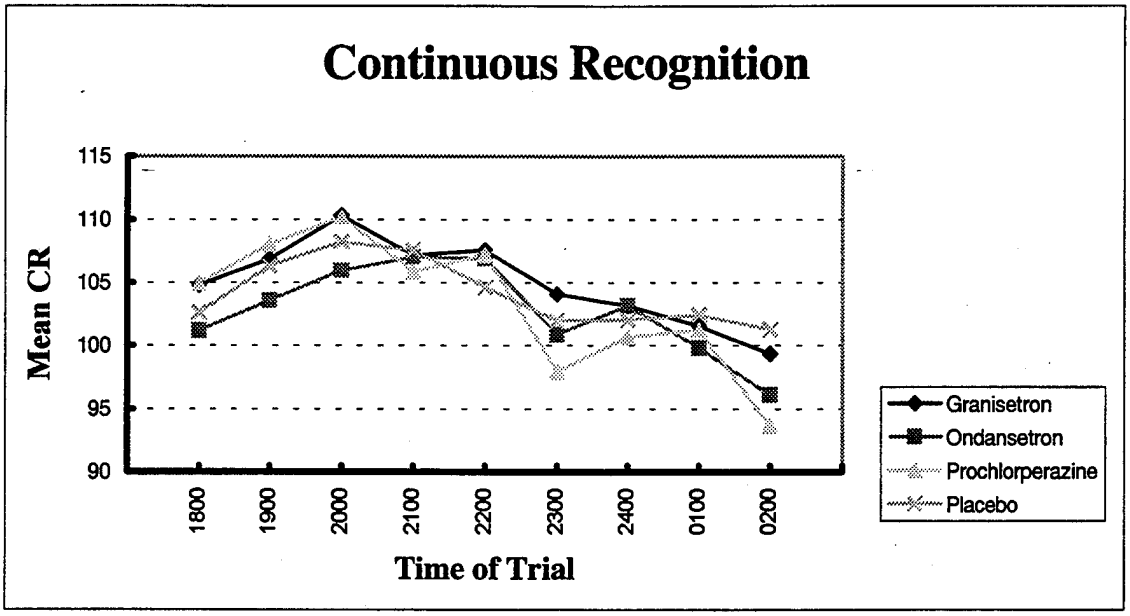

Figure 3.2.4-1: Continuous Recognition Correct Response (CR)
Trial = p < .0001

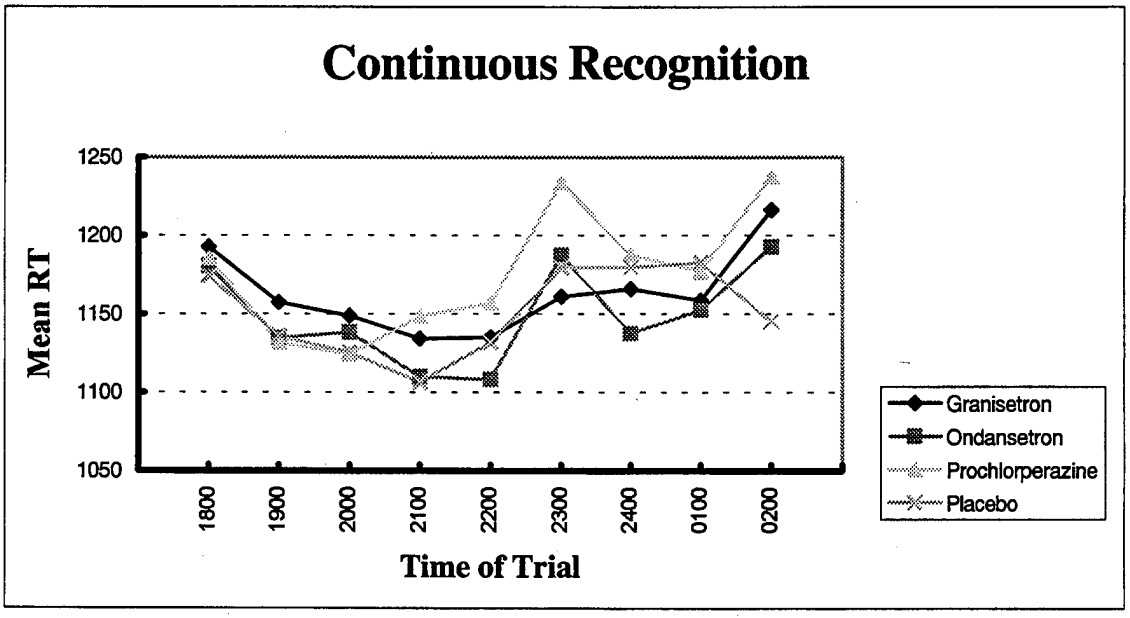

Figure 3.2.4-2: Continuous Recognition Reaction Time (RTmsec), correct trials
Trial = p < .001

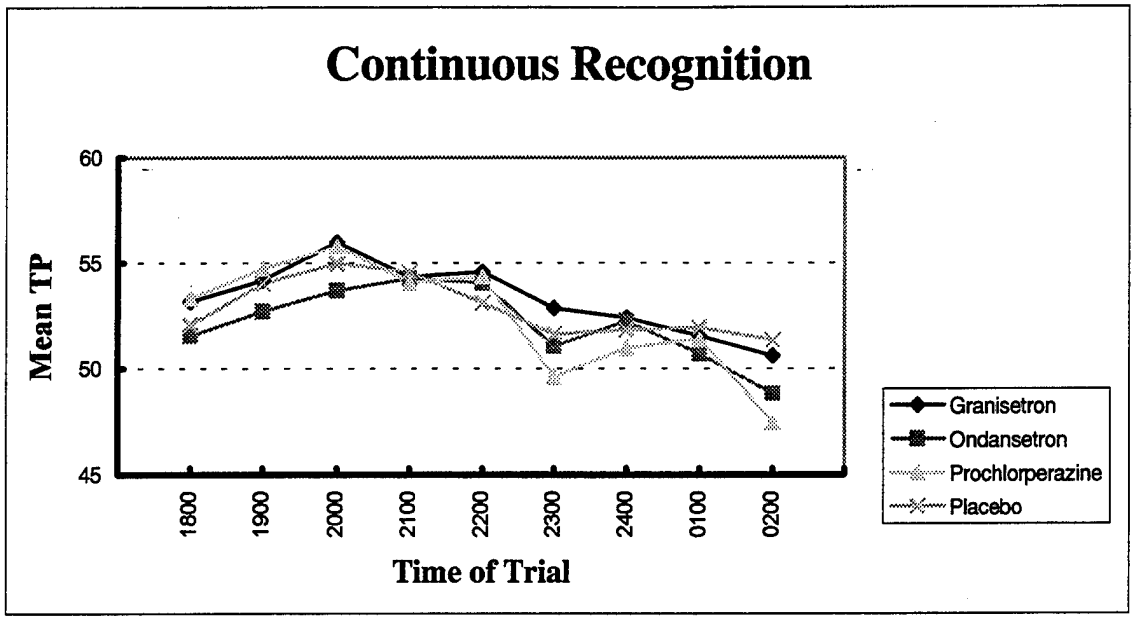

Figure 3.2.4-3: Continuous Recognition Throughput (TP)
Trial = p < .0001

3.2.5 Grammatical Reasoning - The *Grammatical Reasoning* test demonstrated no statistically significant drug main effects and no drug by trial interactions. Performance on the variables of interest (accuracy, reaction time, and throughput) was relatively flat over the first six trials with a fatigue effect becoming apparent only after trial number six. There were positive control effects evident after trial six for accuracy and throughput but these were nonsignificant. A by-trial effect, presumably reflecting fatigue and/or circadian dyschronization, was again prominent over time and highly significant for all three variables: accuracy (p<.0001), reaction time (p<.0001), and throughput (p<.0001) **Figures 3.2.5-1, 2, & 3.**

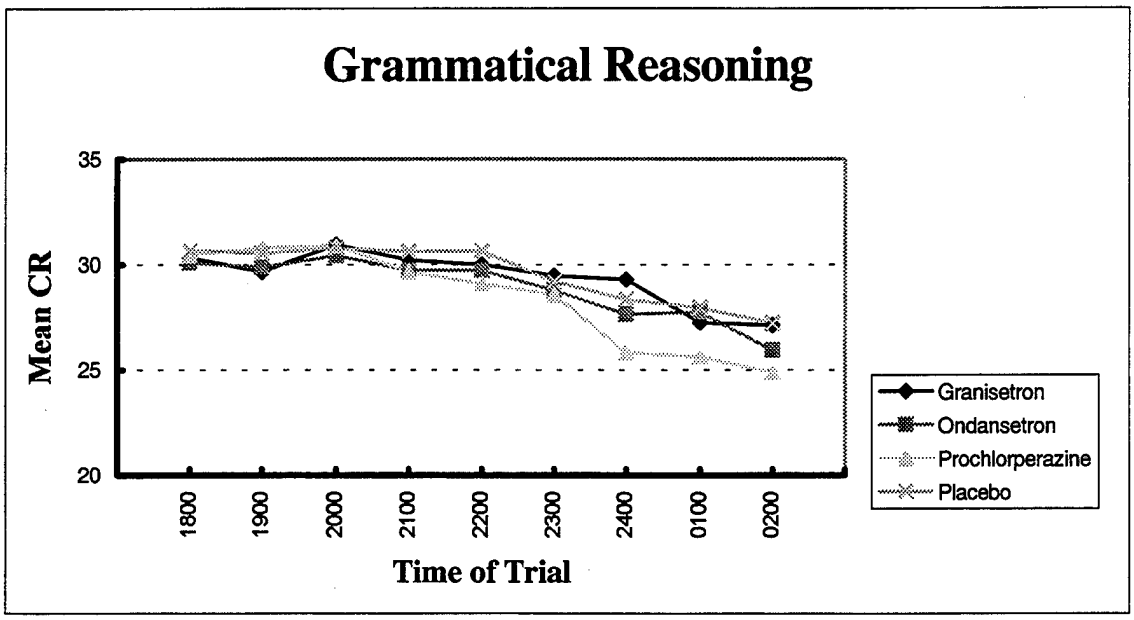

Figure 3.2.5-1: Grammatical Reasoning Correct Response (CR)
Trial = p < .0001

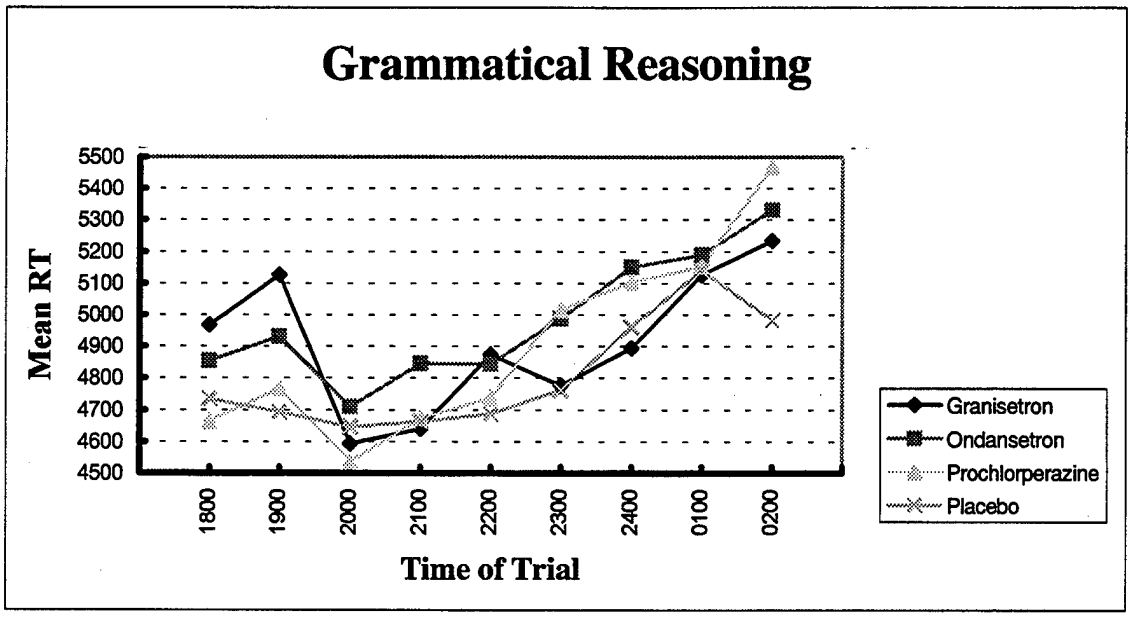

Figure 3.2.5-2: Grammatical Reasoning Reaction Time (RTmsec), correct trials
Trial = $p < .0001$

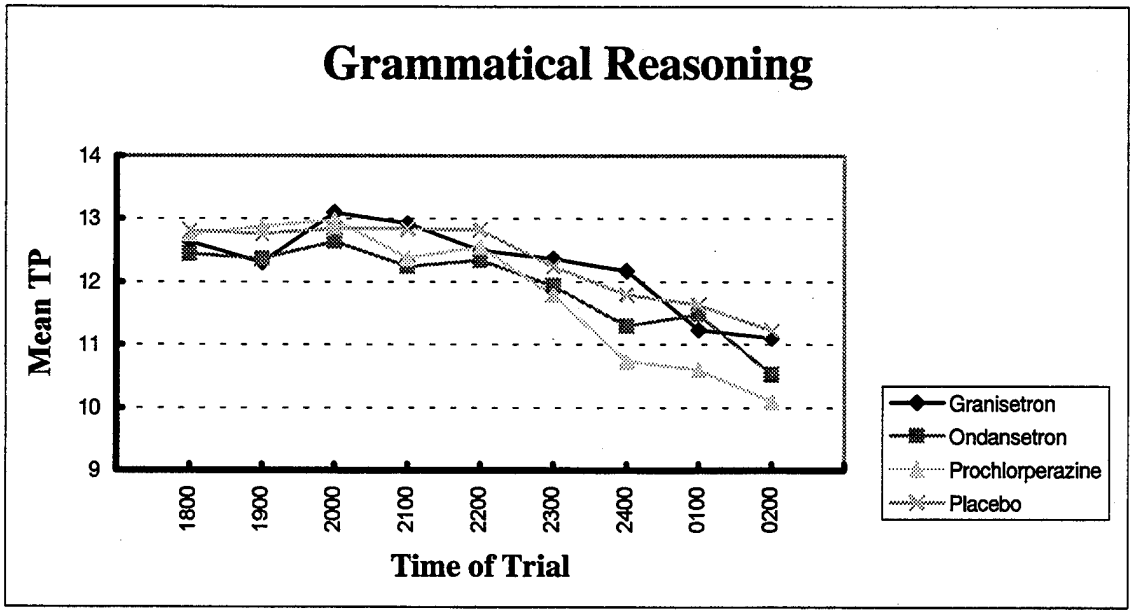

Figure 3.2.5-3: Grammatical Reasoning Throughput (TP)
Trial = $p < .0001$

3.2.6 Ordinal Comparisons - Ordinal comparisons were performed on the PAB results at approximate peak serum-drug levels (i.e. trial 4 @ 2100 h). Drug conditions were ranked (1 = best to 4 = worst) by subject for 22 of the 23 dependent measures. RMS tracking error was not included because of high performance instability. A nonparametric Friedman's test for matched data was performed on each of the 22 dependent variables to test for drug effects. No significant differences were found. The ranks were then averaged over the dependent variables for each subject and drug to compute aggregate ordinal scores. An ANOVA was applied to these

aggregate data to test for drug effects and was nonsignificant. In an effort to improve sensitivity of testing, head-to-head comparisons of granisetron v. ondansetron were also accomplished in a similar manner (i.e. only the two target drugs were ranked). A sign test was also nonsignificant for each of the 22 dependent measures and for the aggregate result, **Figure 3.2.6-1.**

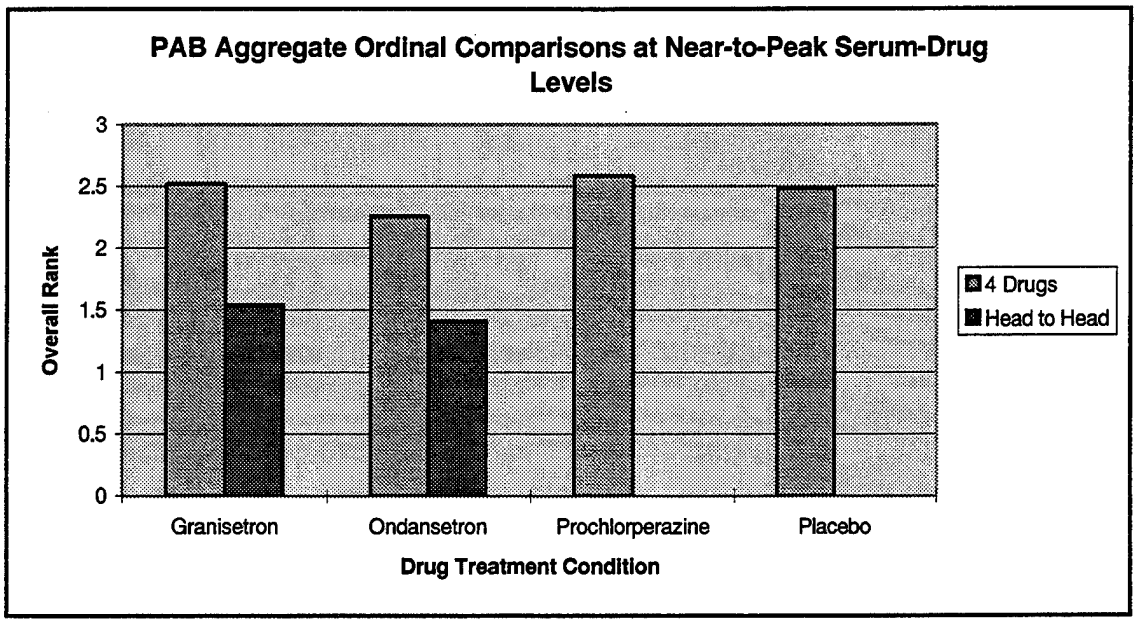

Figure 3.2.6-1: Aggregate Ordinal Comparisons at Trial 4 n/s

3.3 Complex Cognitive Performance Tests - Two different complex tasks were employed during the experimental trials. The Terminal Radar Area Control (TRACON) performance task was used to assess drug and fatigue effects on novel learning. The DSO Analog task was employed to determine possible effects of these same stressors on a previously trained, complex task.

3.3.1 TRACON - *TRACON* was inserted to provide a "real world", relatively complex task with ease of data collection and reasonably objective output measures. TRACON was also used to fill predetermined time periods where there would have been gaps in the activity and possibly alertness of the subjects. The use of TRACON permitted some assessment of drug and fatigue effects on original learning since the subjects received no pretraining on this task. The relative novelty of TRACON compared to the PAB seemed to sustain a high level of subject motivation. Results for the number of aircraft handled indicate a positive learning trend over trials and test sessions ($p<.0001$) masking any fatigue effect, **Figure 3.3.1-1.** Drug treatment main effects were not significantly different from the placebo (control) condition. The scores for individual subjects were highly variable, and except for the granisetron group, demonstrated a consistent trend with apparent learning over trials and test days **Figure 3.3.1-2.** Here also, the effects of fatigue were masked and there were no differences between the treatment conditions. All data points are expressed as treatment group mean scores.

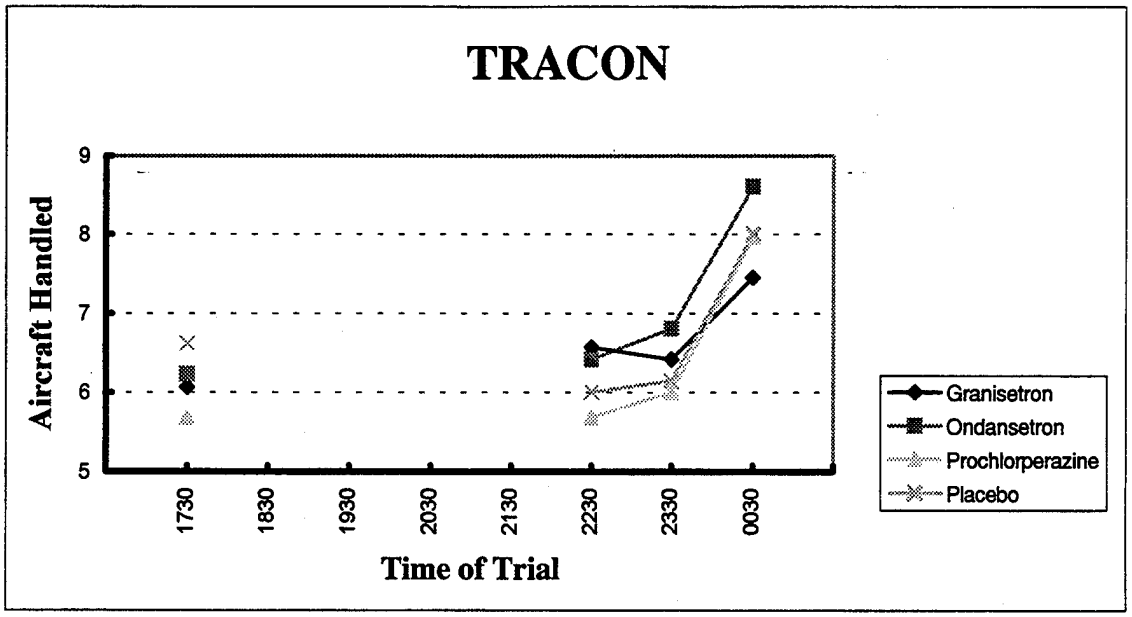

Figure 3.3.1-1: TRACON Aircraft Handled
Trial = $p < .0001$

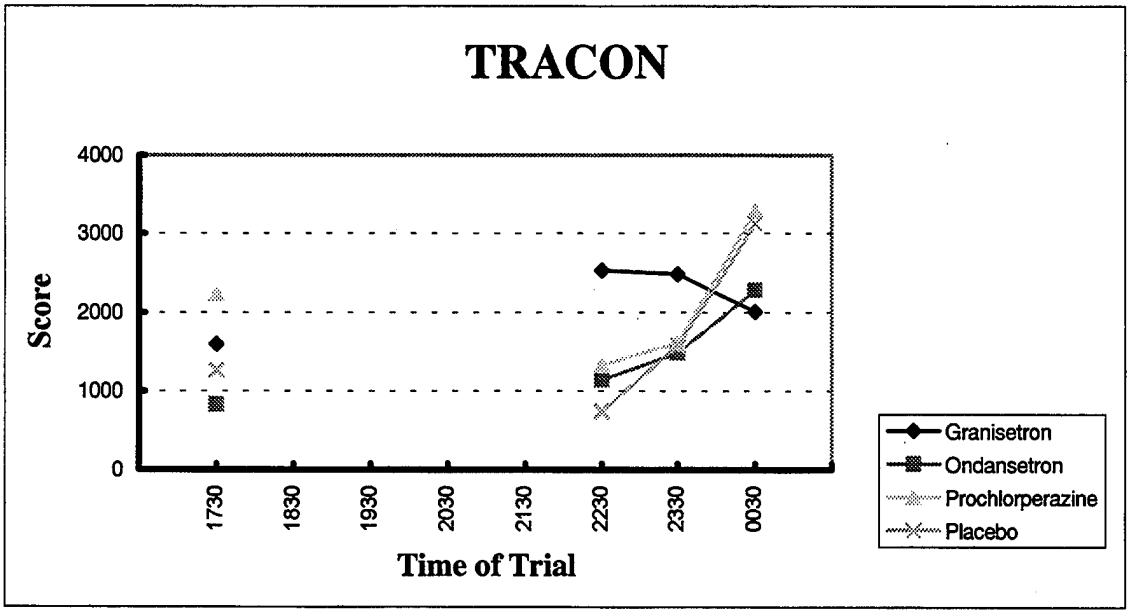

Figure 3.3.1-2: TRACON Score
Trial = $p < .0001$

3.3.2 DSO Analog - The *Analog* was developed to evaluate an operationally relevant, complex task. This task is a synthetic representation of the functions performed by a B-1B Defensive Systems Officer (DSO). The central objectives of this demonstration were to develop task demands similar to those required of the DSO tasks and to evaluate the sensitivity of a complex task to performance degrading influences. This was an initial testing of the Analog task. Therefore, multiple dependent measures were taken to fully assess the sensitivity of this task to drug and trial effects and to assist with future design modifications of the Analog. There were a

total of 49 dependent measures collected. These ranged from measures of the number of mouse clicks performed to more operationally relevant measures such as threat identification, selection of the correct defense, enemy attacks, hits and overall defender performance.

Because of system failures, data from the first group of eight subjects was unusable. Also, four subjects (bottom 25%) from Groups II and III were excluded because of poor performance reflected by the inability to achieve positive scores as compared to the 12 subjects who were able to learn the task. This failure to achieve reasonable mastery of the task is demonstrated graphically in **Figure 3.3.3-1** where individual subjects are plotted as a function of trials. Data for each time point are averaged across all four treatment conditions. Based on the poor results from these four subjects, it seems probable they are from a different population than those who achieved a reasonable skill level on the task.

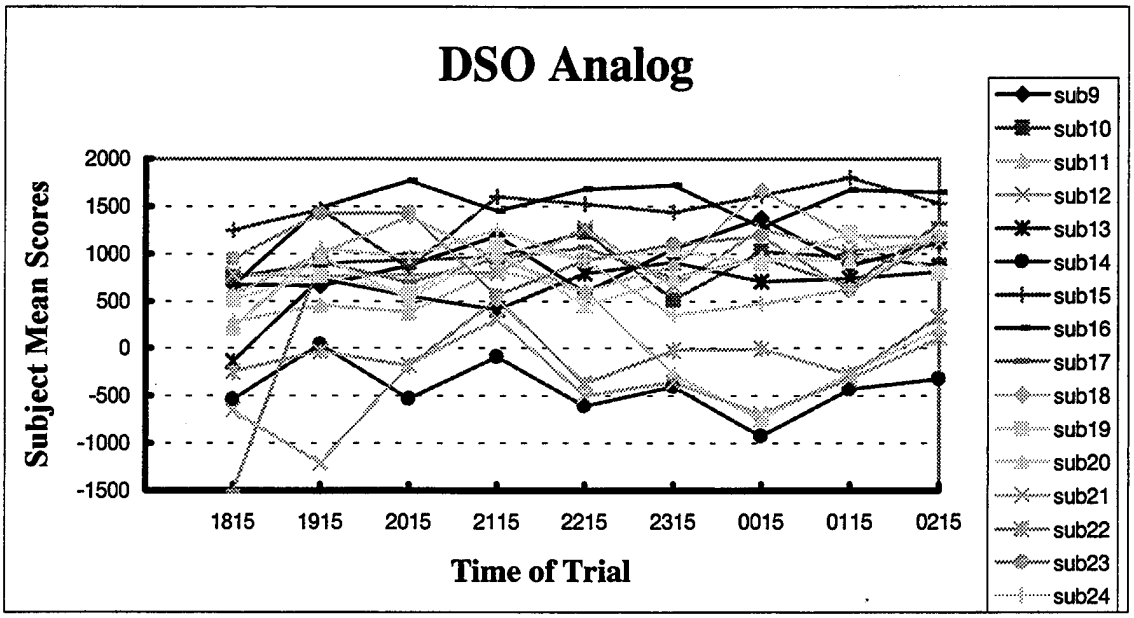

Figure 3.3.3-1: DSO Analog Subject Scores (graphic results only)

The general pattern of results was that the treatment drugs had very little or no effect on performance. There were only two (out of a possible 49) significant main effects of drugs. Neither of these results allow for rational interpretation in that the placebo group performed dramatically worse that than any of the drug treatment groups. On the other hand, many of the dependent measures demonstrated significant trial effects ($p<.05$). It would be unwieldy and beyond the scope of this report to present figures for each measure. Two examples of trial effects related to variables more central to learning v. synthetic task design and which capture overall performance v. contributory factors to overall performance are presented below.

Figure 3.3.2-2 provides mean total points by trial ($p<.01$) for each treatment condition. As can be seen, there appears to be a substantial warm-up effect followed by generally small performance improvements after trial two.

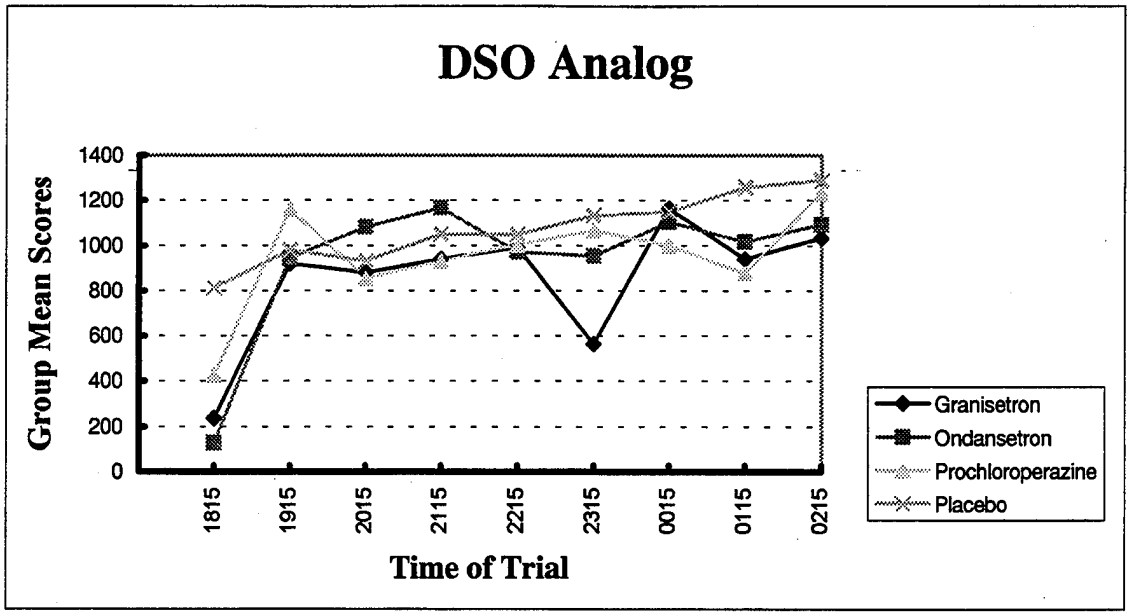

Figure 3.3.2-2: DSO Analog Group Scores
Trial = $p < .01$

Similarly, **Figure 3.2.2-3** shows the number of times the enemy successfully penetrated and launched weapons that impacted upon the target vehicle. Again, performance is generally improving across trials and clearly the most dramatic effect is between trials one and two.

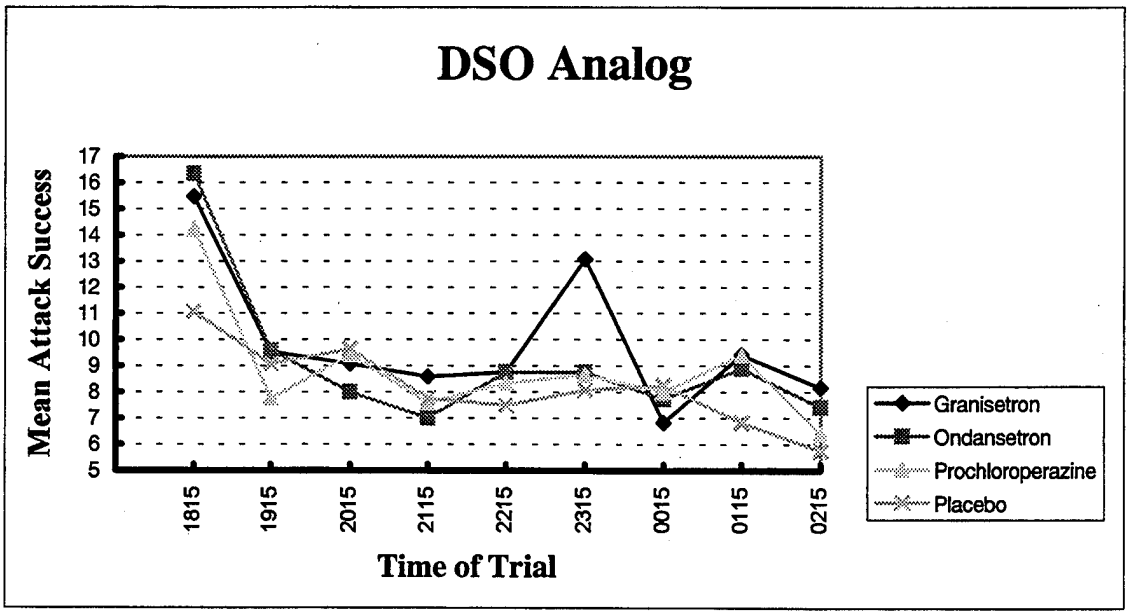

Figure 3.2.2-3: DSO Analog Attack Success
Trial = $p < .01$

As was generally expected regarding the acquisition of a complex, novel task, substantial learning effects were present after the 15 pre-training trials, and task difficulty associated with opportunities for varied learning strategies resulted in poor performance stability well into the testing. Although the variation associated with some of the measures is more narrow, the general pattern is clear - there were no drug effects. Based on chance alone (@ $p<.05$), one would expect to find approximately 2.5 significant events out of 49 dependent measures. For drug-by-trial interactions (viewed in isolation), similarly, one would expect 2.5 of 49. In fact, there were only two drug main effects and one drug-by-trial interaction. In contrast, there were numerous significant trial effects (27 out of 49 dependent measures) reflecting warm-up, a modest learning effect over repetitions and a presumed masking of any fatigue effects.

3.4 Affective State, Vigilance, and Fatigue - Two separate measurement techniques were used to assess changes in affective state and vigilance, a computer version of the commonly used Profile of Mood States (POMS) (McNair, 1971) and a computerized implementation of the Visual Analogue Scale (VAS), (Monk, 1989). In addition to the baseline condition, approximately (1830 h), data were collected only during intervals when blood samples were drawn (i.e. 1930 h, 2030 h, 2130 h and 0130 h). This was planned to assist with the confirmation of any drug induced mood and/or vigilance effects through blood serum results.

3.4.1 Profile of Mood States - *POMS* data are presented as standardized T scores after the Table of T Score Norms for College Students as provided in the POMS Manual (McNair, 1971). There were no significant drug main effects on any of the six POMS scales and there were no significant drug-by-trial interactions. Three of the six POMS scales did result in significant by-trial effects consistent with expectations regarding the subjects' fatigued state. These were Fatigue-Inertia ($p<.0001$), Vigor-Activity ($p<.0001$), and Confusion-Bewilderment ($p<.0001$), **Figures 3.4.1-1, 2, & 3.**

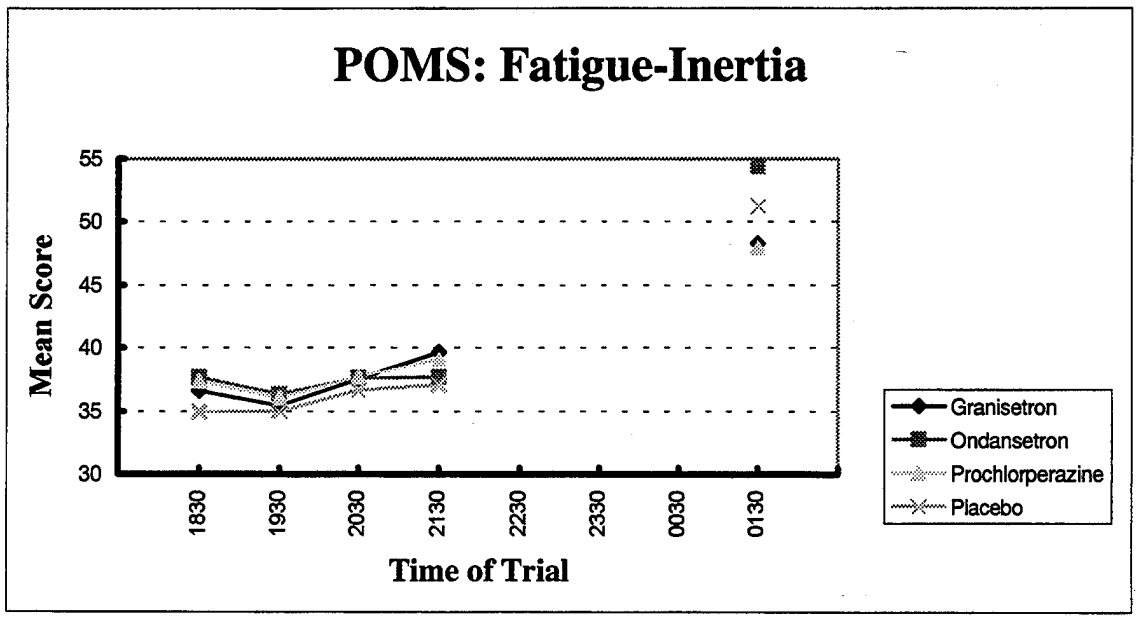

Figure 3.4.1-1: POMS, Fatigue-Inertia
Trial = $p < .0001$

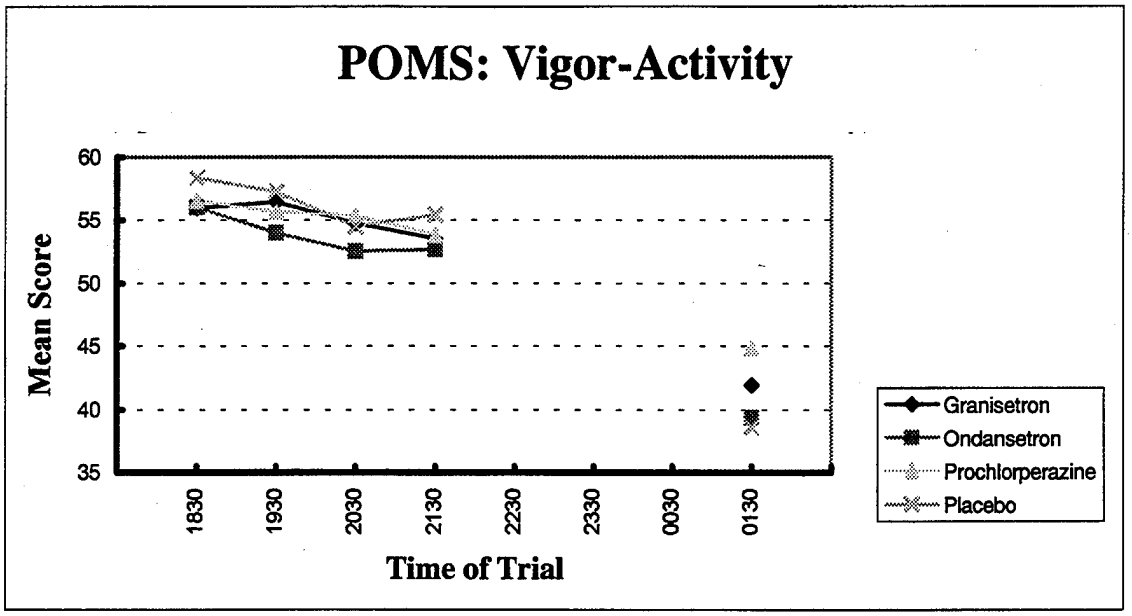

Figure 3.4.1-2: POMS, Vigor-Activity
Trial = $p < .0001$

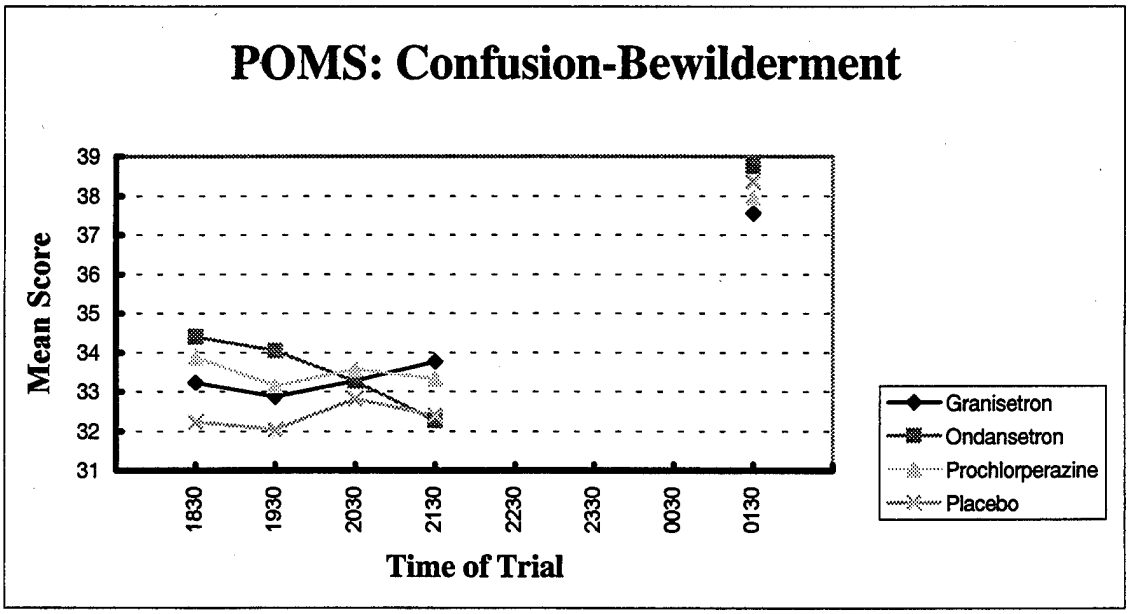

Figure 3.4.1-3: POMS, Confusion-Bewilderment
Trial = $p < .0001$

The Tension-Anxiety results were also significant for trials ($p<.005$), **Figure 3.4.1-4**. Scores seem to follow a U-shaped function if interpolated for the missing trials where POMS was not administered. These results possibly reflect novel demands of the test environment at the beginning of a test session to include venous catheter insertions and a heightened level of tension or excitement when nearing the end.

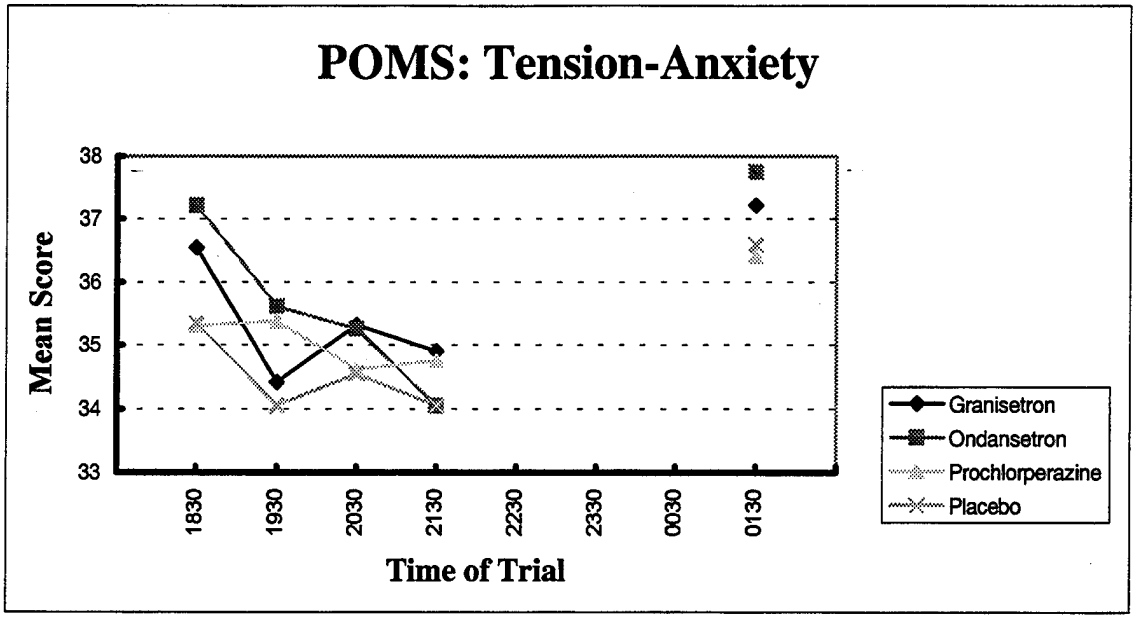

Figure 3.4.1-4: POMS, Tension-Anxiety
Trial = $p < .005$

Statistical results for Depression-Dejection and Anger-Hostility were nonsignificant for drug or trial effects, **Figures 3.4.1-5 & 6.** As a matter of speculation, it would seem that heightening of these emotions does not appear very adaptive or relevant to paid volunteers who are mentally healthy and performing under relatively non threatening conditions.

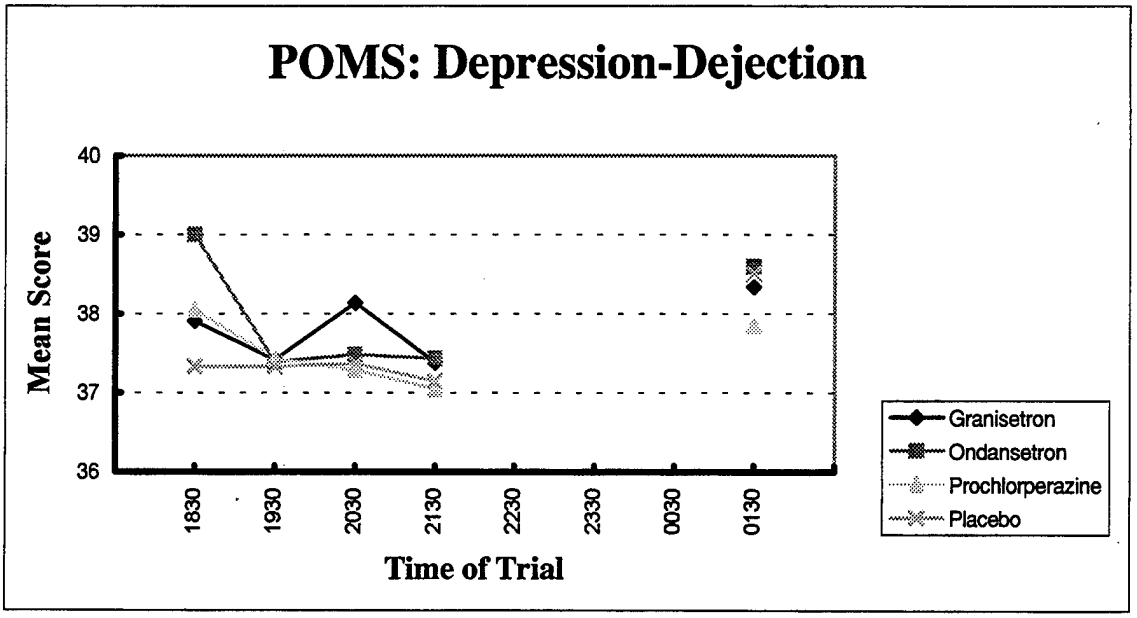

Figure 3.4.1-5: POMS, Depression-Dejection
n/s

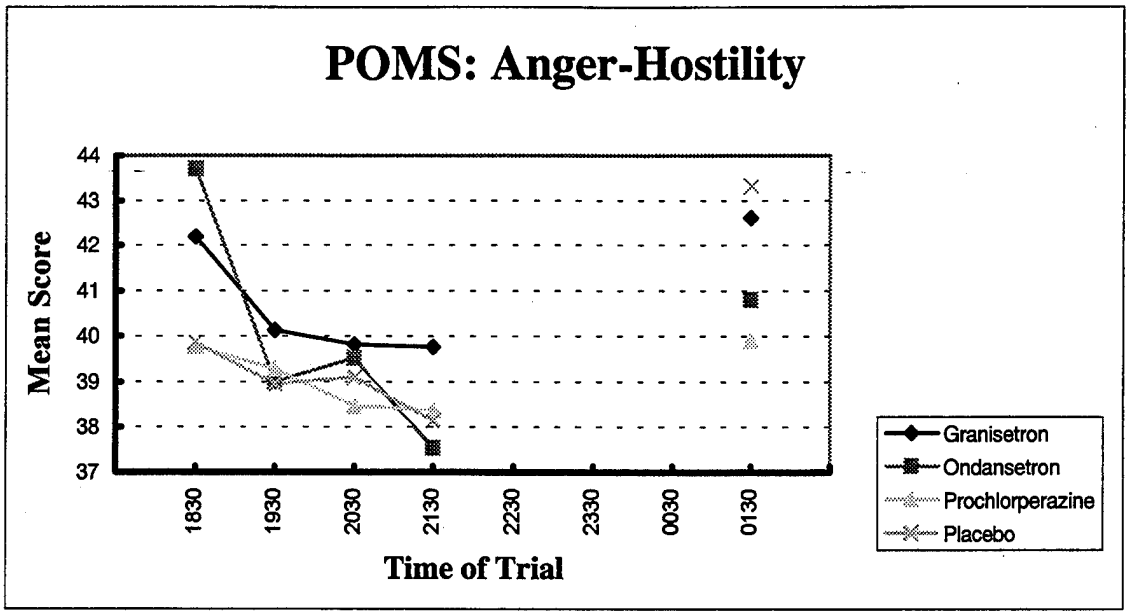

Figure 3.4.1-6: POMS, Anger-Hostility
n/s

In order to provide a single global estimate of affective state, a Total Mood Disturbance (TMD) score has been derived by summing the scores across all six factors (weighting Vigor negatively) after McNair, 1971, **Figure 3.4.1-7**. The TMD score is presumed to be reliable because of the intercorrelations among the six primary POMS factors. The TMD scores over the first four administrations of POMS are intermingled by treatment condition and relatively flat in trend. Only on the last administration is there a substantial change from baseline presumably due to fatigue and/or circadian desynchronization. It is of some interest to note that on this last trial the prochlorperazine group shows the least overall mood disturbance.

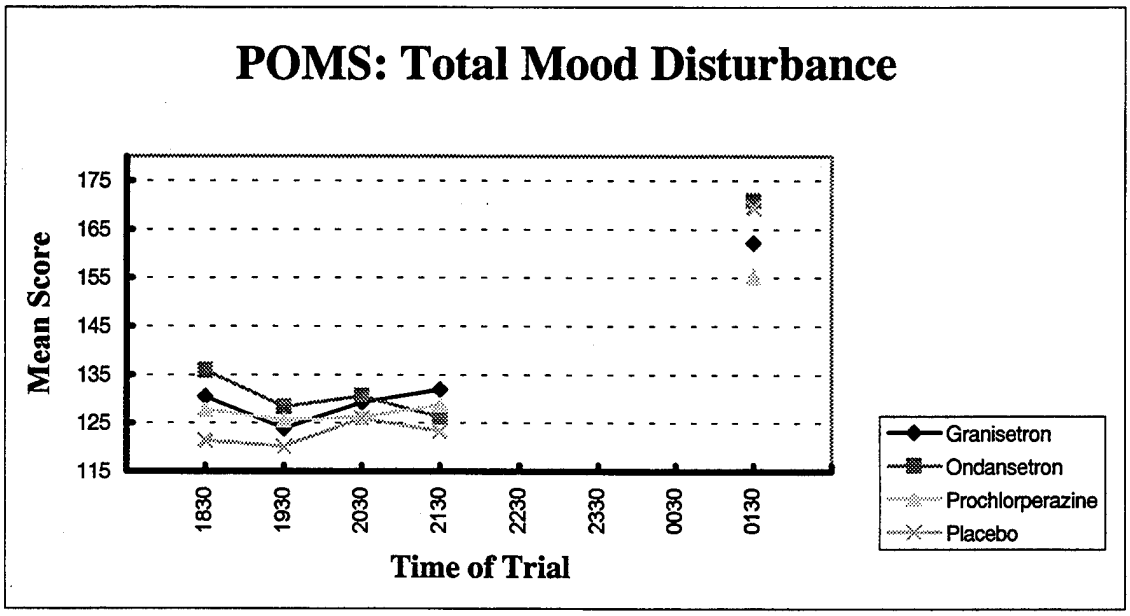

Figure 3.4.1-7: POMS, Total Mood Displacement
(graphic results only)

3.4.2 Visual Analog Scale: Affective State and Vigor - Similar results were obtained from the *Visual Analog Scale* (VAS) of affect and vigor. There were no significant drug main effects or drug-by-trial interaction effects. There were highly significant ($p<.0001$) effects by-trial for seven (Alert, Tense, Effort, Happy, Weary, Calm, and Sleepy) of the eight VAS scales, **Figures 3.4.2-1, 2, 3, 4, 5, 6, 7.**

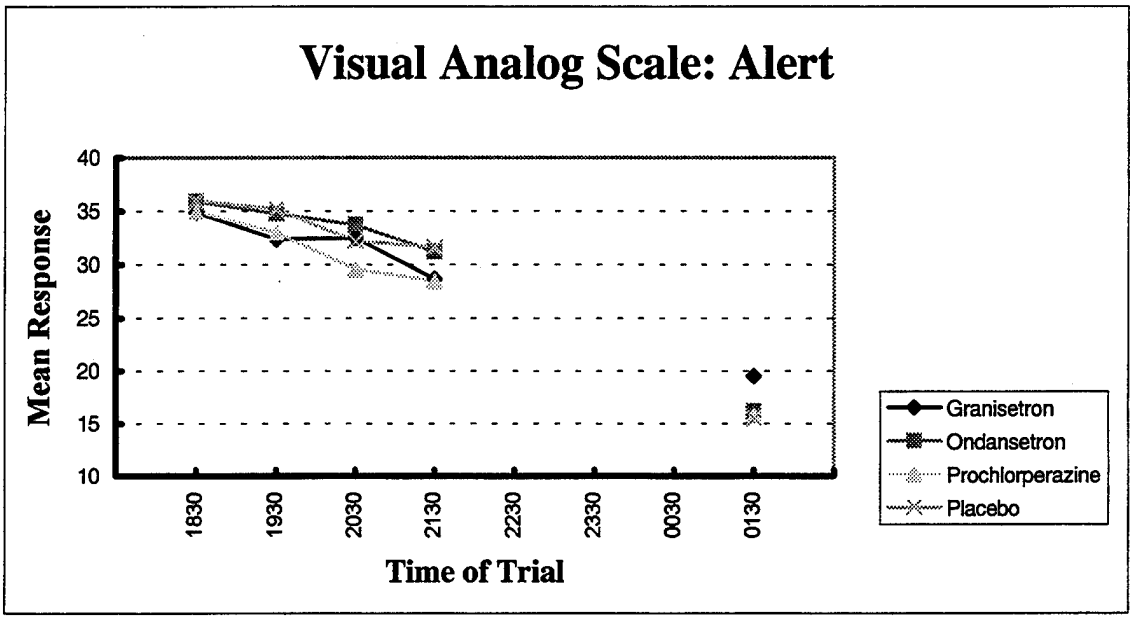

Figure 3.4.2-1: VAS, Alertness
Trial = $p < .0001$

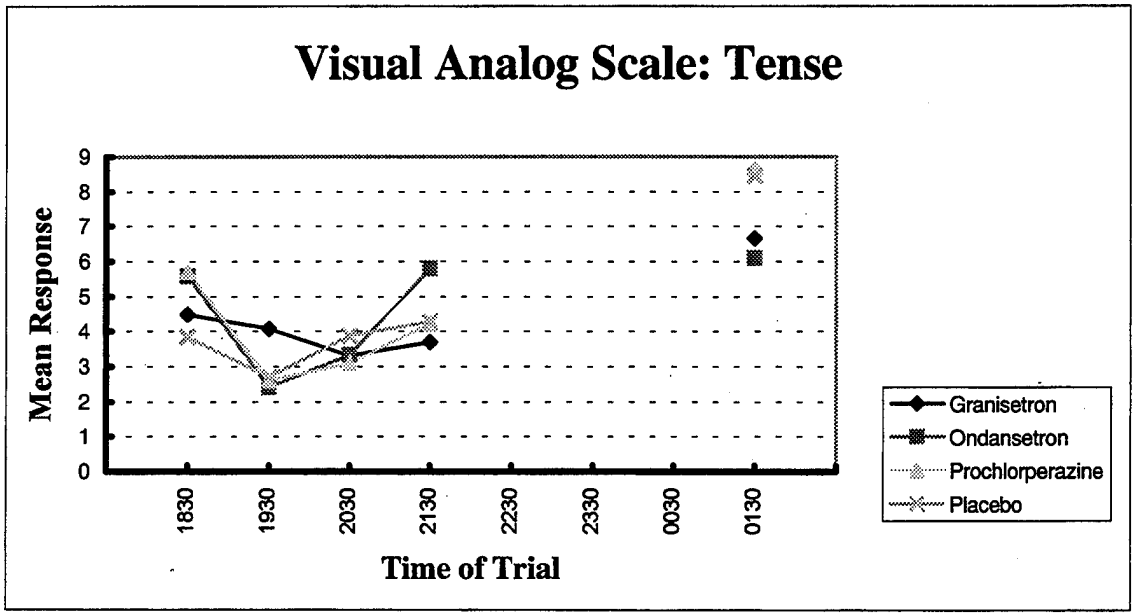

Figure 3.4.2-2: VAS, Tension
Trial = $p < .0001$

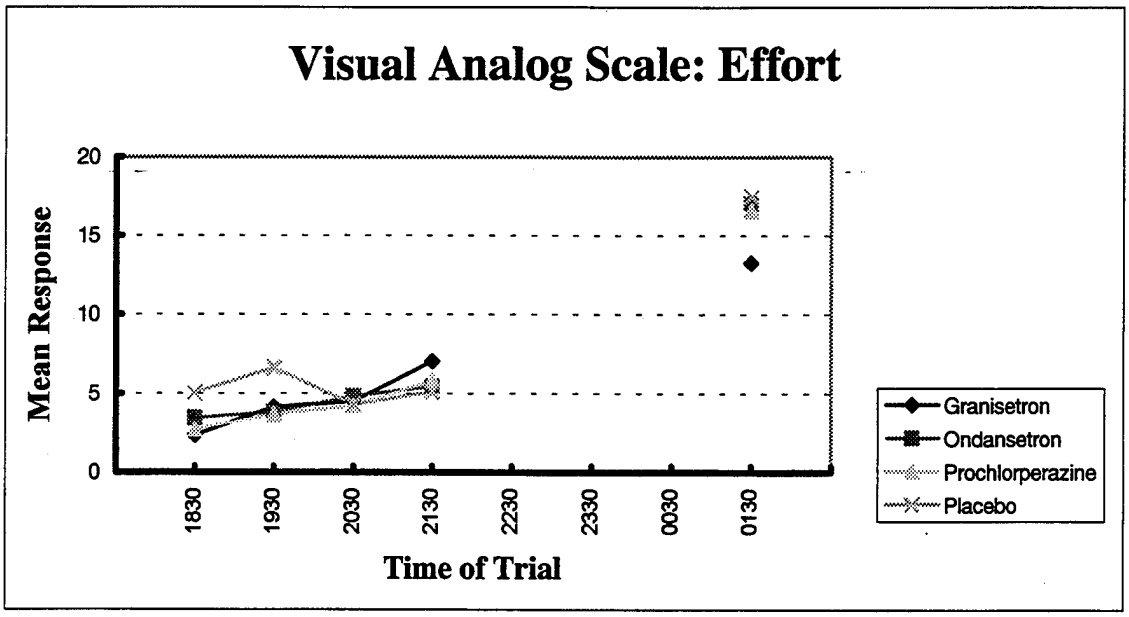

Figure 3.4.2-3: VAS, Effort
Trial = p < .0001

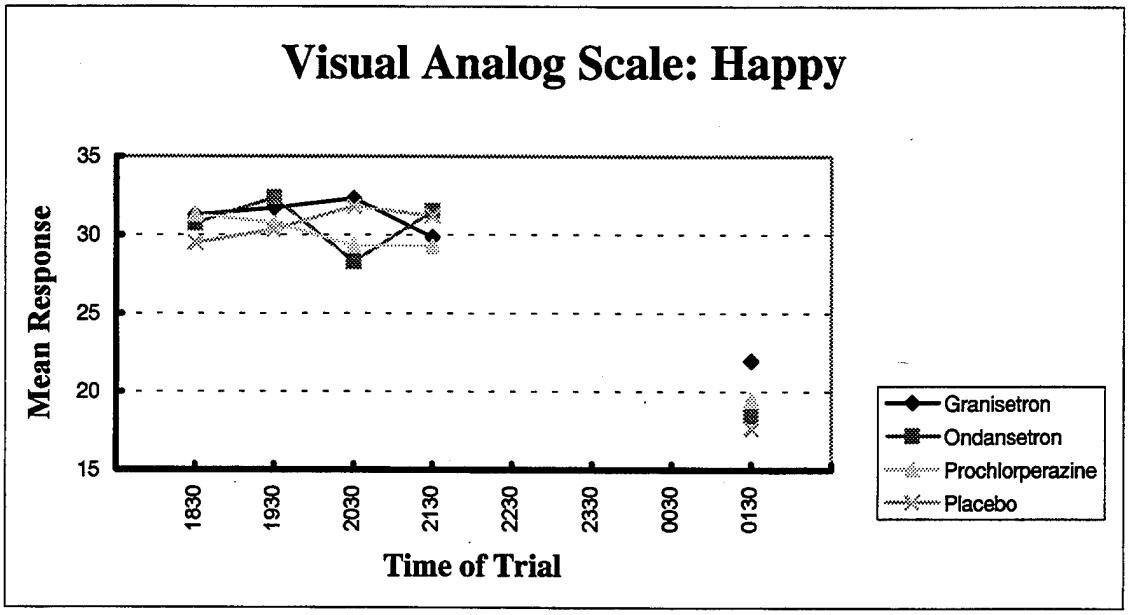

Figure 3.4.2-4: VAS, Happiness
Trial = p < .0001

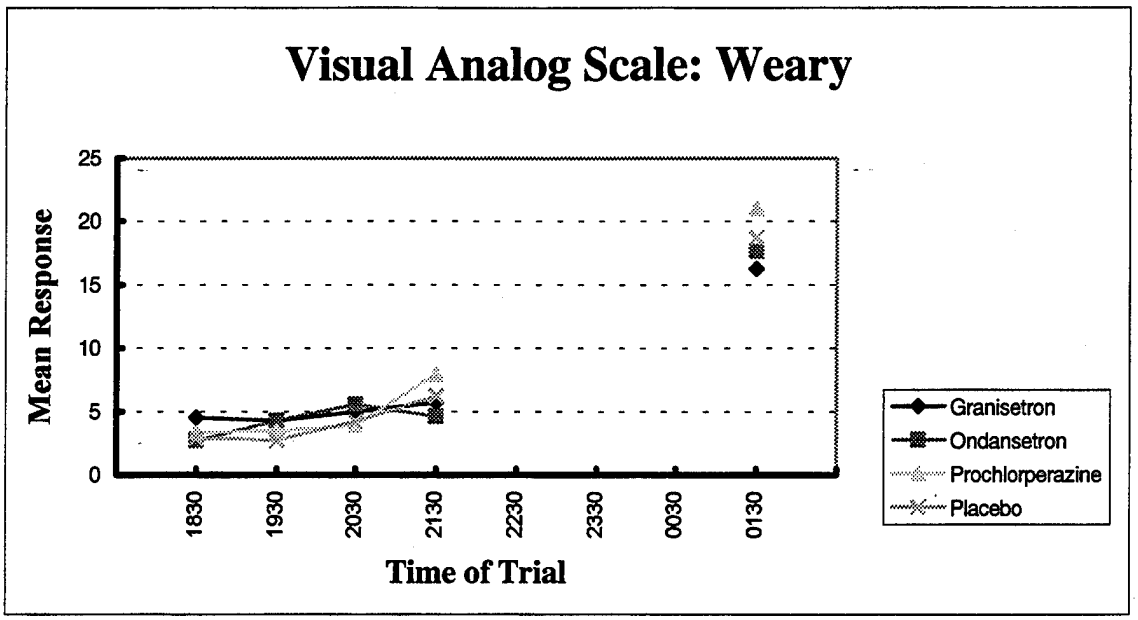

Figure 3.4.2-5: VAS, Weariness
Trial = p < .0001

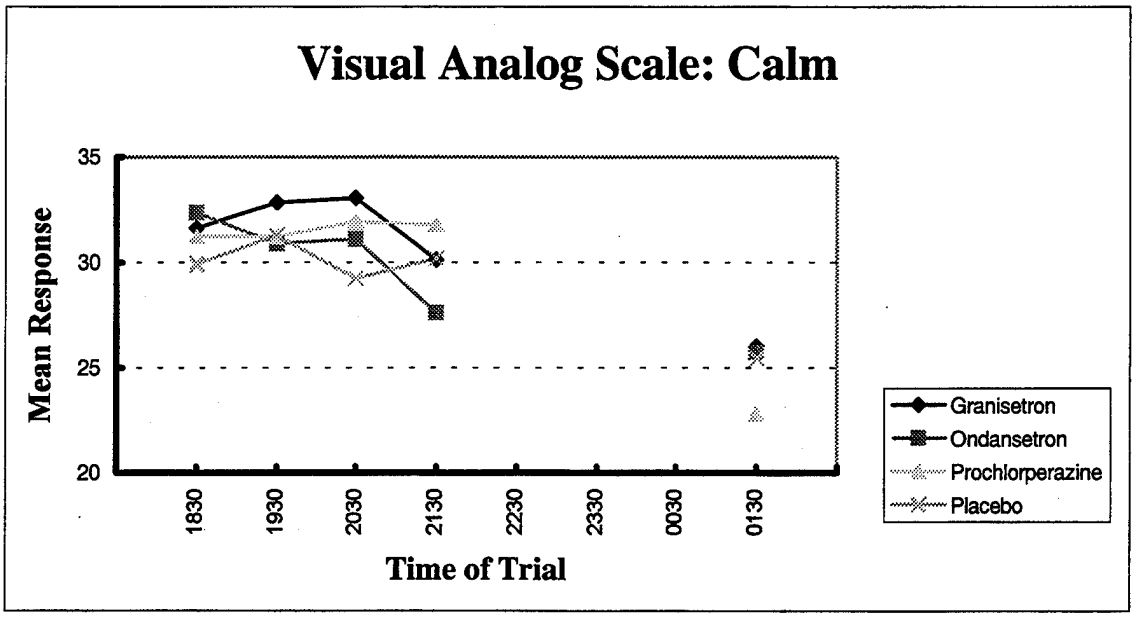

Figure 3.4.2-6: VAS, Calmness
Trial= p < .0001

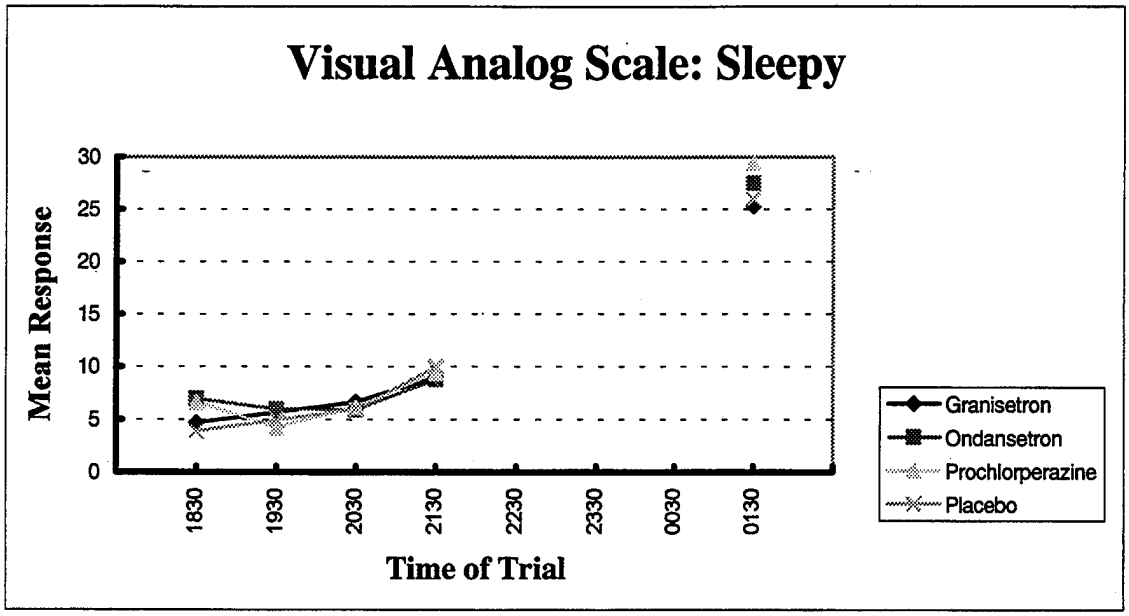

Figure 3.4.2-7: VAS, Sleepiness
Trial = $p < .0001$

Interestingly, results from the VAS: "Sad" scale were not statistically significant over trials, **Figure 3.4.2-8.** This outcome is consistent with that obtained on the POMS: "Depression-Dejection" scale and suggests a similar rationale (i.e. "Sad" was not an appropriate emotion for young, healthy, paid, military subjects) for the lack of a fatigue influence.

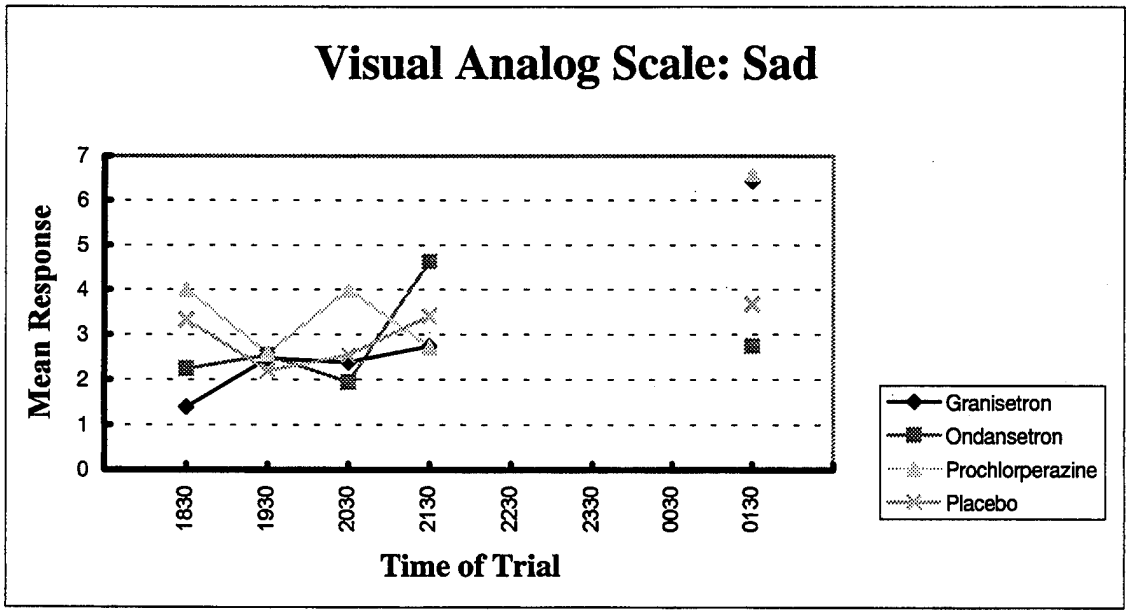

Figure 3.4.2-8: VAS, Sadness
n/s

Transformation of the eight unipolar scales to global indices of affect and vigor graphically summarize the findings from the VAS. Rating scales related to feelings or affective state

(Happiness, Sadness, Calmness, and Tension) are combined to generate an index of Global Affect (GA), **Figure 3.4.2-9**. Ratings for the scales related to subjective activation or (Vigor Alertness, Sleepiness, Effort, and Weariness) are combined to create an index of Global Vigor (GV), **Figure 3.4.2-10**. These results are normalized on a scale of 0-41 which represents the number of character spaces (42 spaces) between the extremes ("very little" to "very much") on the analogue scale. This was done for ease of comparing global results, GA and GV, with results from the eight unipolar data subsets. GA and GV were computed as follows:

GA = [(Happy) + (Calm) + (2 x 42) - (Sad) - (Tense)] / 4

GV = [(Alert) + (3 x 42) - (Sleepy) - (Effort) - (Weary)] / 4

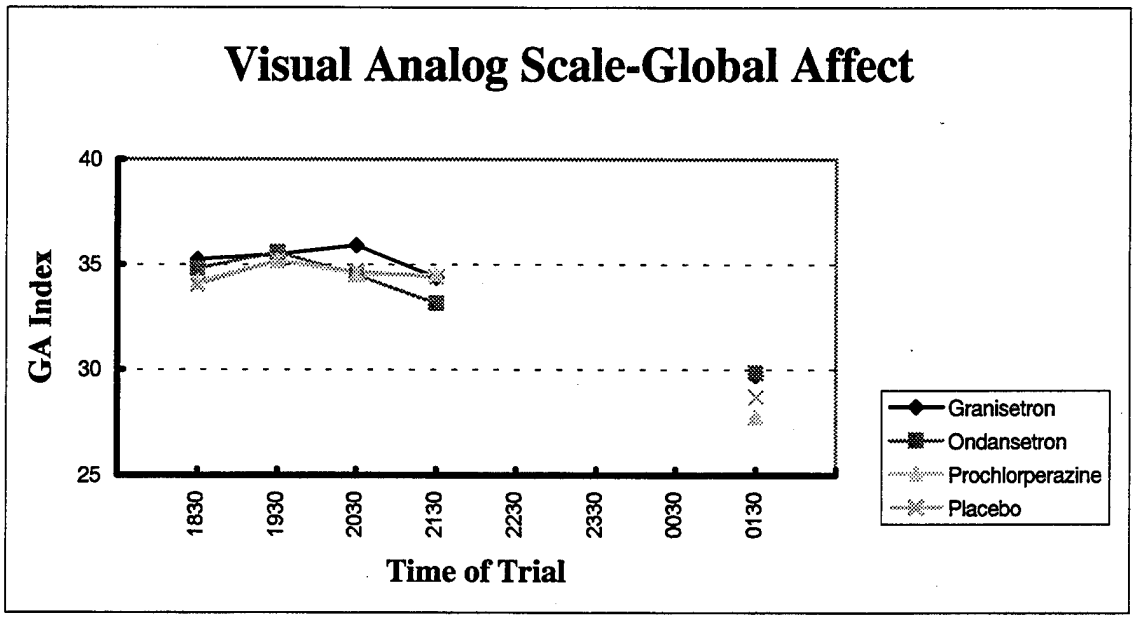

Figure 3.4.2-9: VAS, Global Affect
(graphic results only)

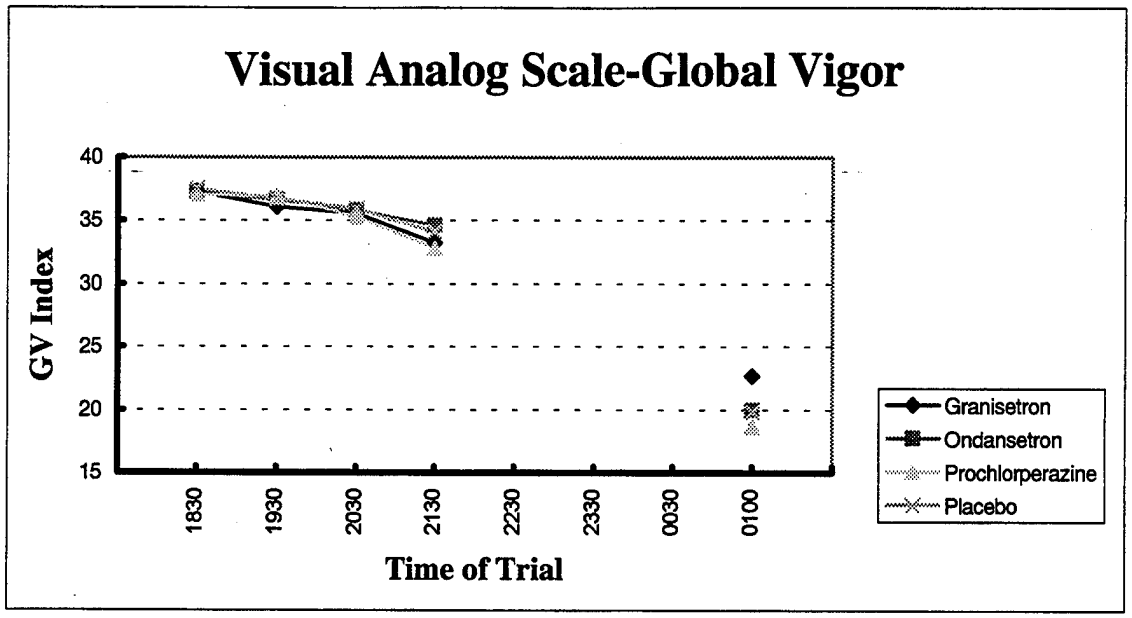

Figure 3.4.2-10: VAS, Global Vigor
(graphic results only)

3.4.3 Vigilance - Results from the *Vigilance* test were largely unremarkable. Accuracy was captured in the number of correct responses for both signal and noise stimulus presentations. The performance by this group of subjects over the four treatment conditions averaged approximately five correct responses for every six signal presentations with minor fluctuations over trials. Similar results can be observed in the data which represent the number of correct responses to the presentation of a noise condition. There were 19 noise signals presented during each of the trials and subjects averaged approximately 18.5 correct responses. Neither of these metrics were significant for the main effects of drugs or trials (fatigue), **Figures 3.4.3-1 & 2.**

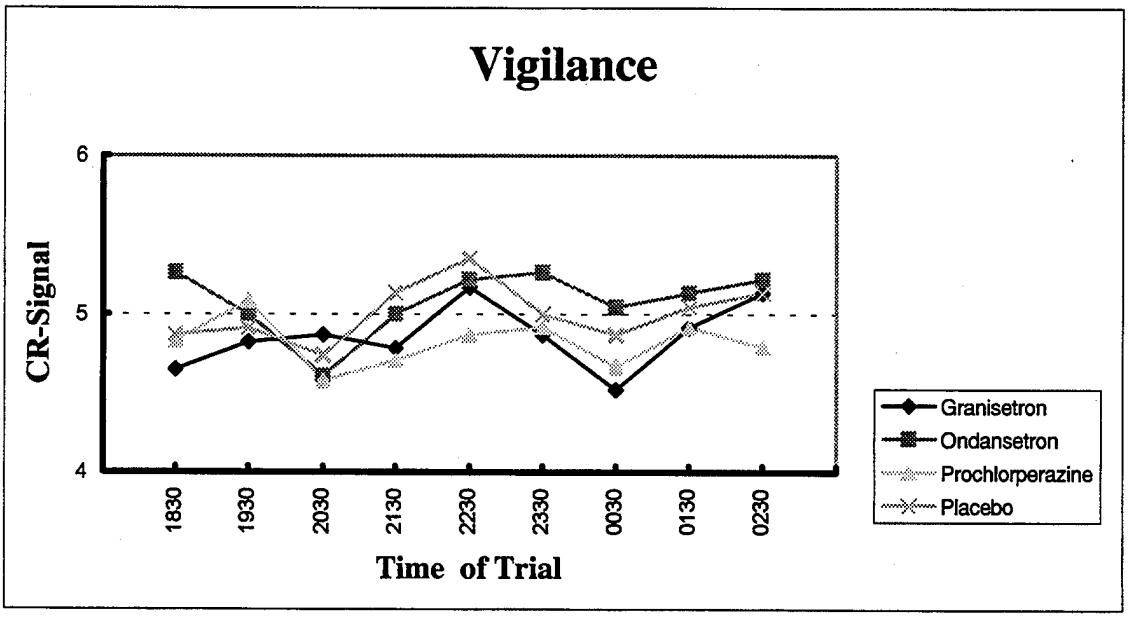

Figure 3.4.3-1: Correct Response (CR) to Signal
n/s

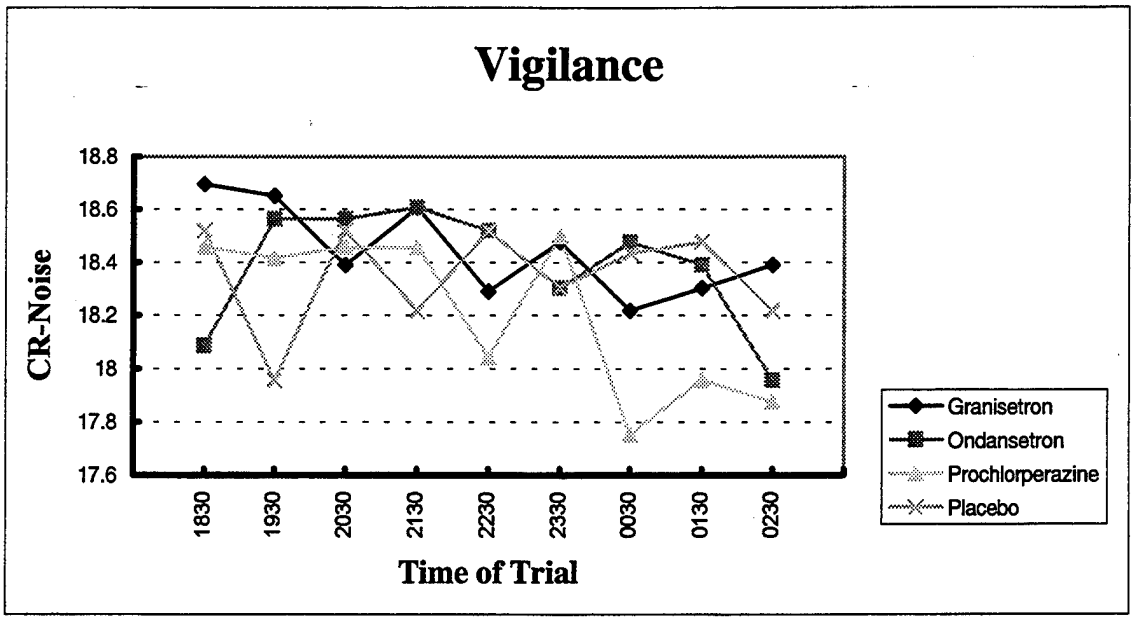

Figure 3.4.3-2: Correct Response (CR) to Noise n/s

The average response times were significant for a by-trial effect ($p<.0005$) and demonstrated graphic evidence of a slight decline over the first six trials, followed by recovery to near baseline performance by the last trial. Clear evidence of a fatigue effect is not apparent in these data and performance improvement over the last three trials does not provide a basis for rational interpretation, **Figure 3.4.3-3**. This is the only laboratory performance test which did not provide evidence of a pronounced fatigue effect. In fairness to others who have found this test to be sensitive to a variety of stressors, this version of the Vigilance Test repeated the order of stimulus presentation on each trial and any fatigue or drug effects were more than likely masked by the learning of the stimulus presentation set.

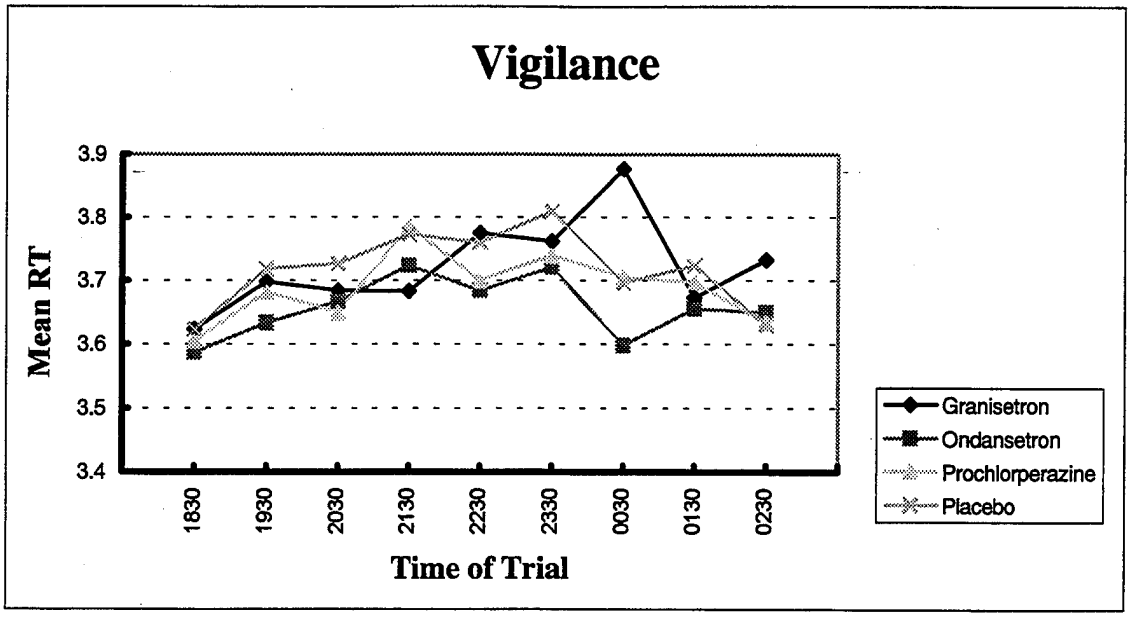

Figure 3.4.3-3: Vigilance Reaction Time (RTsec), correct trials
Trial = p < .0005

3.4.4 Fatigue - Subjective ratings from the *SAM Fatigue Scale* (1= low to 7= high) show a dramatic increase in fatigue over time with scores between one and two at baseline and steadily climbing to five or above during the final presentation of this rating scale. The various treatment conditions produced remarkably similar results across each of the nine trials. There seems to be a small fatigue increase in the positive control group during the middle trials and a slight mitigation reflected in the ratings on the final trial for each group. There were no significant drug effects or drug-by-trial interactions related to the SAM Fatigue Scale, **Figure 3.4.4-1.**

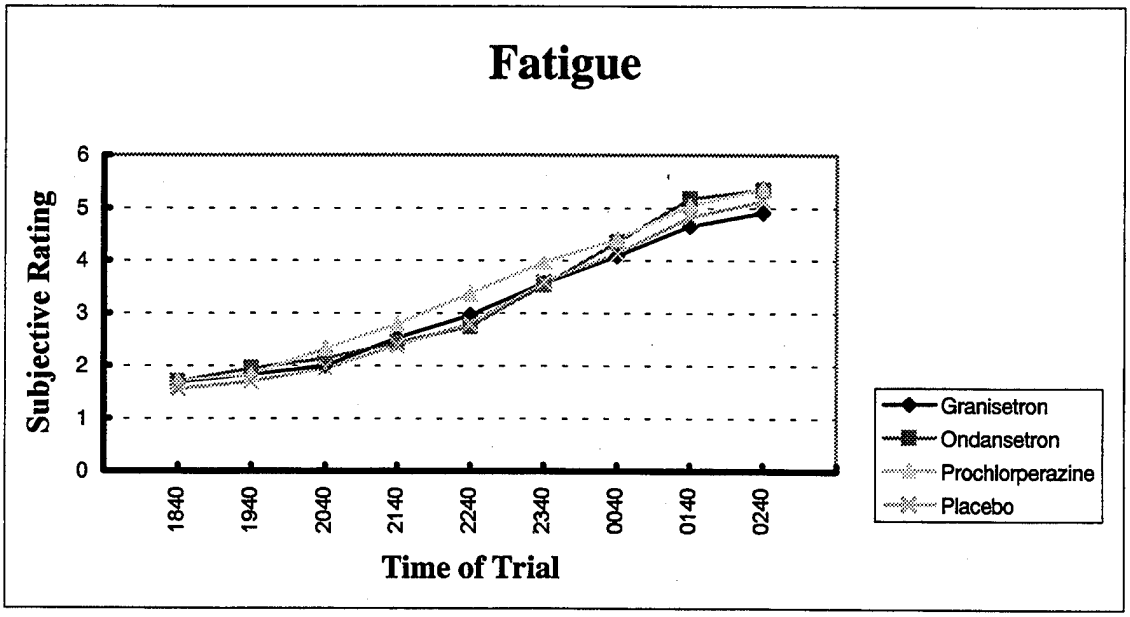

Figure 3.4.4-1: Fatigue Rating (1 = Fully Alert to 7 = Completely Exhausted)
Trial = p < .0001

3.5 Psychophysiological, Physiological, and Physical Measures - Serum-drug, temperature and sleep data were collected to provide additional experimental control and assist with the interpretation of results. Symptoms data included number, severity, degree of impairment and a physicians assessment of the relationship between symptoms and treatment conditions. Critical Flicker Fusion thresholds were collected as an inferential indicator of visual system/CNS processing.

3.5.1 Sleep - *Sleep* hours and quality sleep were recorded on an Activity Log, **Appendix E**, and confirmed electronically by actigraphic recording. Statistical analysis of pre-test and post-test sleep periods for both the manual log entries and the actigraph recordings revealed no differences between the treatment groups. Correlation (Z Transform) between logged sleep hours and actigraph sleep hours was significant at $p<.01$. The pre-test sleep activity log range was 8.1 h. to 8. 5 h. with a mean of 8.2 h, **Figure 3.5.1-1**. As might be expected following a disrupted circadian pattern, the post-test sleep period was more variable across treatment groups, but nevertheless nonsignificant, exhibiting a range of 6.5 h. to 8.1 h. with a mean of 7.6 h. With regard to sleep quality for both pre-test and post-test periods, there were no differences between treatment groups based on activity log results or actigraph recordings. On a scale of 1-3 (1 = worse than normal to 3 = better than normal) the mean logged quality of pre-test sleep was 1.55 with a range of 1.38 to 1.87 while actigraph counts ranged from 1097 to 1326 with a mean of 1218, **Figure 3.5.1-2**.

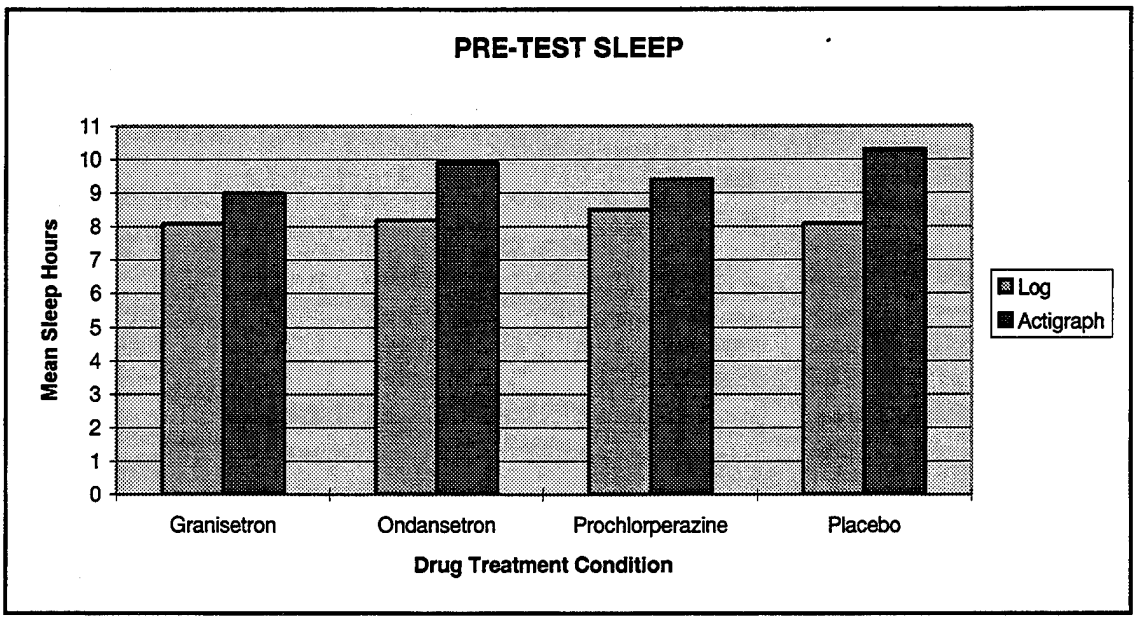

Figure 3.5.1-1: Pre-test Sleep Hours
n/s

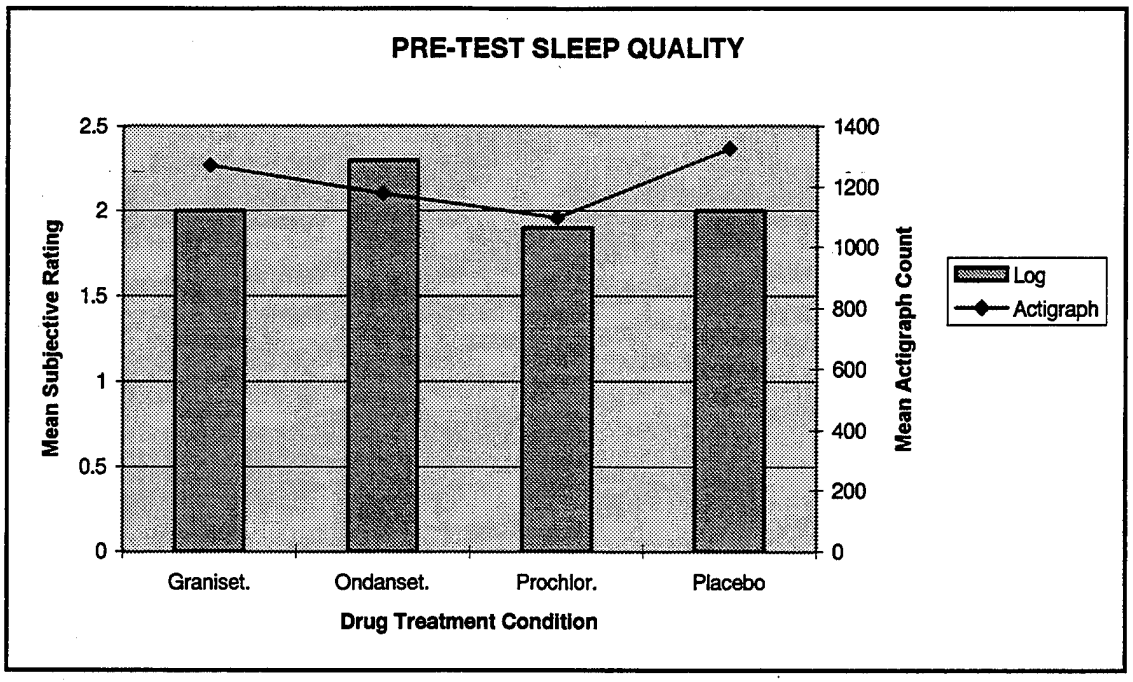

Figure 3.5.1-2: Pre-test Sleep Quality
n/s

3.5.2 Critical Flicker Fusion - *Critical Flicker Fusion (CFF)* frequency is presumed to decrease in response to conditions which decrement visual system function and/or lower arousal or activation level in the central nervous system. Subjects in this study were tested using both eyes and were required to manually adjust the flicker frequency of two red light bars by turning a knob on the side of the hand held viewer. Three threshold measurements were taken from a subject every hour during a test session. These intra-subject measurements were averaged to minimize confounding due to individual subject lability. Results for three of the treatment conditions demonstrate a slight increase in arousal between trials 1 and 2, followed by a general decline in CFF threshold frequency reflecting decreased arousal and increasing fatigue. There is a rise in threshold associated with each of the four treatment conditions on the final trial. Overall, the decrease in CFF threshold by-trial was significant ($p<.0001$) each of the individual CFF measurements and consequently the average of three sample measurements taken each hour. The slope of these curves and last trial recovery are similar to the results from the Performance Assessment Battery, described previously. If indeed CFF is a measure of CNS arousal, then it may be sensitive to mental fatigue and demonstrate results similar to those obtained from tests of memory, reasoning and information processing in general. Again, results from the three drug conditions and placebo are, for the most part, intertwined in moderately declining threshold values until the last trial where subject activation level may improve CFF results - similar to the observations made previously with regard to several of the cognitive performance tests, **Figure 3.5.2-1.**

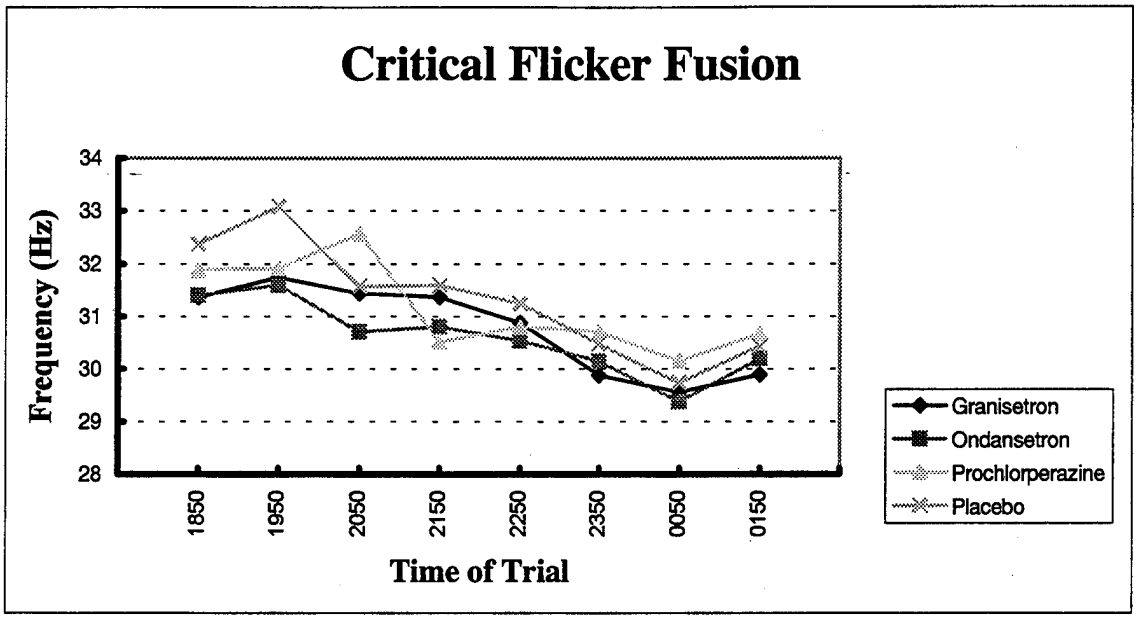

Figure 3.5.2-1: Critical Flicker Fusion Threshold
Trial = $p < .0001$

3.5.3 Blood - *Blood Assays* were used to confirm the presence of active drugs in serum. Thresholds were established through testing of spiked standard curves and empirical determination of a threshold peak at 2 x the baseline noise on the chromatogram. In the first group of subjects there were two instances where laboratory results failed to confirm the presence of drug in the serum of a subject. All data associated with these subjects and test sessions were excluded from the statistical analysis thereby reducing the subject population from 24 to 23 subjects for the ondansetron and granisetron treatment conditions. Serum-drug measurements were limited to four samples per subject per test session. Blood samples were taken during each of the first three hours of testing and a sample was collected at hour six - post drug administration. Limited resources precluded a more exhaustive sampling event schedule. These times were selected to demonstrate a rising serum-drug level over the first two-three hours and evidence drug half life / extinction phase by hour six of testing. An exact peak for each of the target drugs is difficult to pinpoint, but the curves appear to be shifted to the right, with peaks occurring approximately two-three hours after drug administration. Based on the literature, the peaks for granisetron and ondansetron are somewhat extended for this subject population. This may reflect reduced metabolic activity associated with the time of day, a mean subject body weight of 171 lb, non adherence to fasting requirements, and/or the possibility that the opaque capsules used to blind investigators and subjects to the treatment conditions may have caused a delay in the release of drug. Based on these data, both granisetron and ondansetron are presumed to be near half life by hour six, **Figures 3.5.3-1 & 2.**

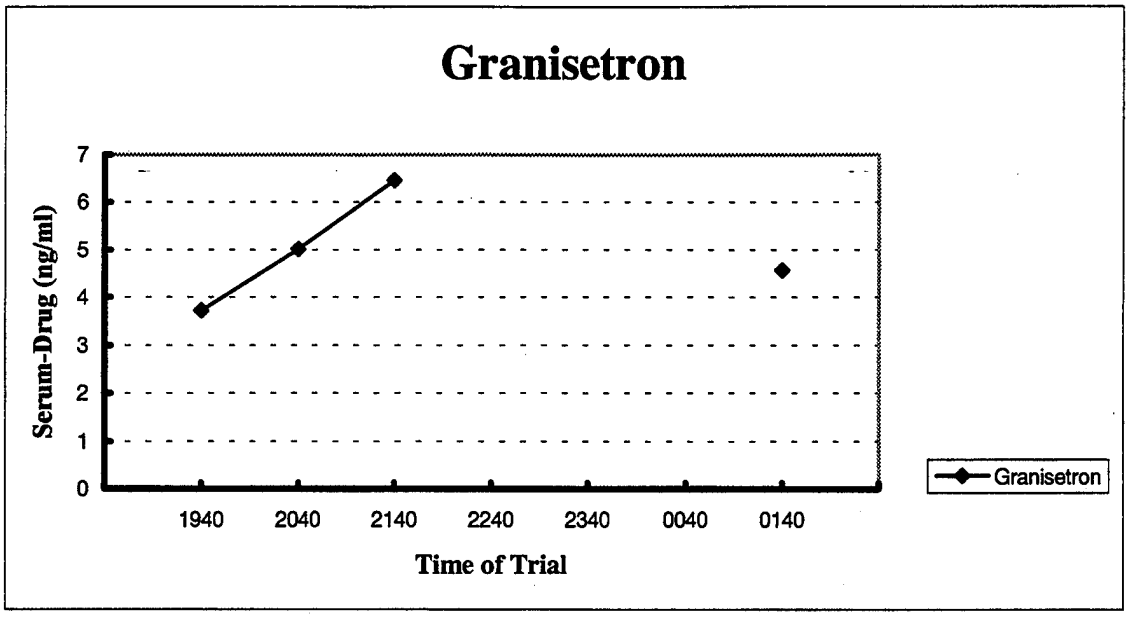

Figure 3.5.3-1: Serum Granisetron Levels
(graphic results only)

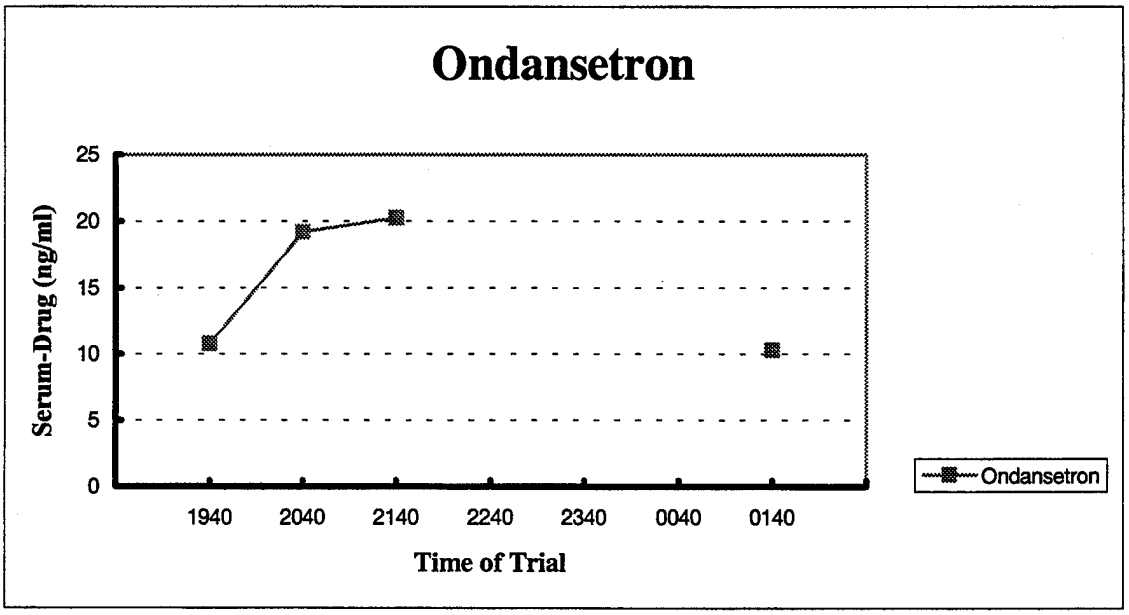

Figure 3.5.3-2: Serum Ondansetron Levels
(graphic results only)

In contrast, the positive control drug, prochlorperazine, shows a rise in serum level between hours three and six. If a standard extinction curve is assumed, the peak appears to occur between hours four and six, **Figure 3.5.3-3.**

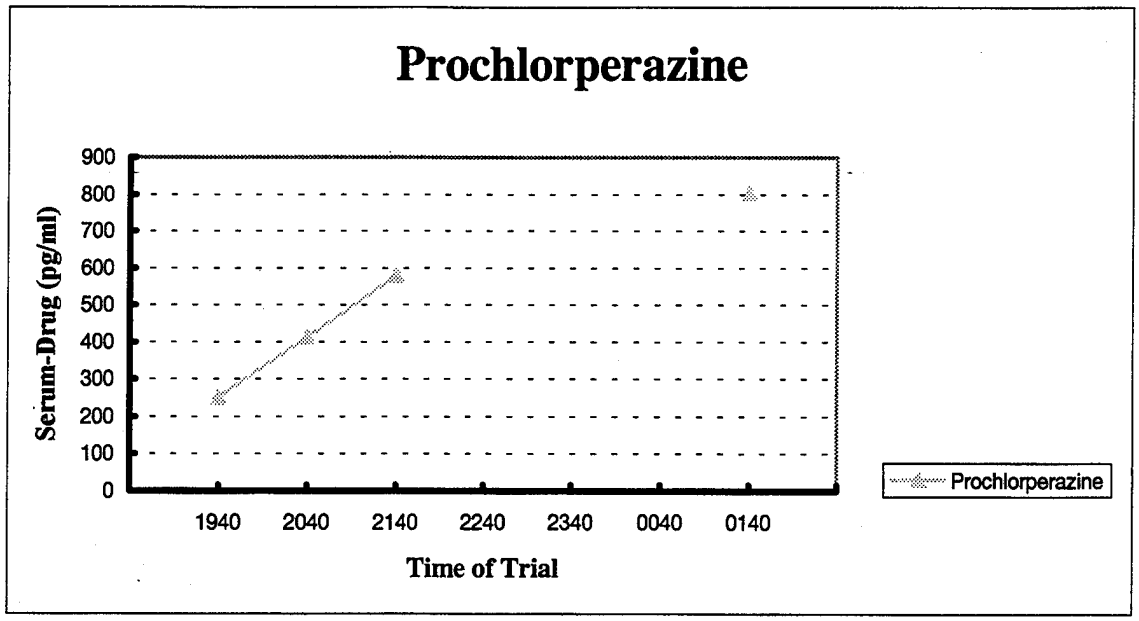

Figure 3.5.3-3: Serum Prochlorperazine (graphic results only)

Variability in the serum-drug levels were, as expected, quite high, stemming from the fact that each subject received a standard dose and there were differences in weight, age and gender among the subjects. Even with limited sampling, individual subject data suggest a standard serum-drug curve, **Appendix F.**

3.5.4 Temperature - Consistent with the anticipated effect of normal circadian rhythmicity , average oral *Temperatures* evidenced a steady and highly significant ($p<.0001$) decline during testing. There were no statistically significant drug main effects and no drug-by-trial interactions detected through the recording of oral temperatures, **Figure 3.5.4-1.**

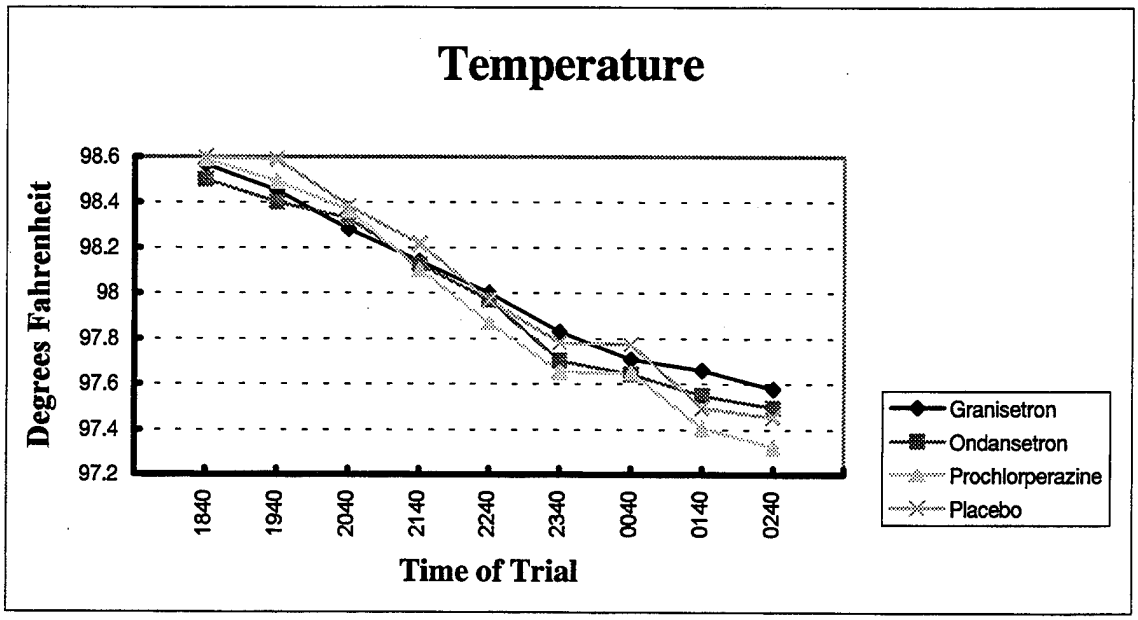

Figure 3.5.4-1: Oral Temperature Change
Trial = $p < .0001$

3.5.5 Symptoms - Symptom checklists were completed by each subject during the test sessions and delayed symptoms checklists were completed to evaluate the interim periods between drug administrations. Of the twenty-six symptoms on the lists, eleven symptoms received positive responses during the test sessions, and 16 delayed symptoms were reported. Of these, only four test session symptoms were reported by more than one subject within a treatment condition (drowsiness, sluggishness, headache and stomach cramp); and only five delayed symptoms were reported by more than one subject within a treatment condition (drowsiness, sluggishness, headache, gas and constipation). At no time were symptoms reported that required medical intervention. No test subjects were eliminated due to an adverse medical event. As a general conclusion (excepting results for drowsiness and sluggishness caused by fatigue), differences in reported symptoms represent a small number of occurrences, inconsistent direction and/or lack of cause and effect relationships.

Summary results, tabulated from the *incidence* of symptoms by treatment condition (during testing), are presented in **Table 3.5.5-1.** Although the incidence of headache is highest in the granisetron group, these results reflect a difference of one subject report when compared to the placebo condition. Similarly, the higher percentage for stomach cramps in the granisetron group represents a difference of two subjects when compared to placebo. Small percentage differences related to the same absolute incidence values reflect the loss of data from one subject (each) from the granisetron and ondansetron groups because of the inability to confirm drug in serum (i.e. granisetron n = 23; ondansetron n = 23; prochlorperazine n = 24 ; placebo n = 24).

Table 3.5.5-1: Symptom Incidence During Testing

	SYMPTOM				
DRUG CONDITION	DROWSINESS	SLUGGISHNESS	HEADACHE	STOMACH CRAMP	COLD
Granisetron	12 (52%)	9 (39%)	5 (22%)	3 (13%)	
Ondansetron	14 (61%)	6 (26%)	2 (9%)	1 (4%)	
Prochlorperazine	17 (71%)	9 (38%)	2 (8%)	1 (4%)	
Placebo	15 (63%)	6 (25%)	4 (17%)	1 (4%)	1 (4%)

Table 3.5.5-1 *con't*: **Symptom Incidence During Testing**

	SYMPTOM					
DRUG CONDITION	MUSCLE CRAMP	MUSCLE TWITCH	FAINTNESS	DISTURBED VISION	DIZZINESS	GAS
Granisetron				1 (4%)	1 (4%)	1 (4%)
Ondansetron				1 (4%)		
Prochlorperazine		1 (4%)	1 (4%)	1 (4%)		
Placebo	1 (4%)		1 (4%)	1 (4%)	1 (4%)	

For purposes of assigning a value reflecting the *severity* of a symptom, subjective assessments were reported on an integer scale of severity from 1 (slight) to 7 (severe). The analysis presented here compares the change in symptom severity from the baseline value. For example, a subject reporting a baseline (prior to drug administration) severity "2" headache at the outset of testing

was considered to have a test related symptom (*incidence*) only if the severity reported later in the testing became worse (i.e. "3" or above). Numerical scores represent the mean of the highest values reported where there were multiple subject reports of a symptom associated with a drug condition. Otherwise, for single subject reports, the numeric score is the highest value reported. Symptoms that continued at the same level of severity or abated after the start of the test session were not considered test related (i.e. were not included in the *incidence*, *severity* or *impairment* data) and are discarded from this analysis.

Symptom Severity During Testing - There were small differences in the reported severity of symptoms by treatment condition, **Table 3.5.5-2**. A cursory assessment of symptom severity by drug condition might suggest a difference in the severity of headache reported by subjects taking granisetron as compared to the other drugs. However, more careful analysis of the raw data reveals that this difference is generated by a single report of an unusually severe headache from one subject.

Table 3.5.5-2: Symptom Severity During Testing[1]

	SYMPTOM				
DRUG CONDITION	DROWSINESS	SLUGGISHNESS	HEADACHE	STOMACH CRAMP	COLD
Granisetron	2.5	2.1	3.0	5.3	
Ondansetron	2.4	3.5	1.0	3.0	
Prochlorperazine	2.6	1.5	1.0	3.0	
Placebo	3.2	3.5	1.0	1.0	2.0

[1] Mean severity (scale: 1=slight to 7=severe)

Table 3.5.5-2 *con't*: Symptom Severity During Testing

	SYMPTOM					
DRUG CONDITION	MUSCLE CRAMP	MUSCLE TWITCH	FAINTNESS	DISTURBED VISION	DIZZINESS	GAS
Granisetron				1.0	1.0	5.0
Ondansetron	1.0		2.0	1.0	1.0	
Prochlorperazine				2.0		
Placebo		1.0	2.0		1.0	

Symptom related *impairment* was reported on a scale between 1 (none) and 5 (severe). The rules for scoring impairment were equivalent to the rules for evaluating severity. An impairment was not considered related to a test condition unless it became worse subsequent to drug administration. Therefore, a subject beginning a test session (prior to drug administration) with a headache causing a grade "2" impairment was not considered to have test related (i.e. drug induced) impairment unless the degree of subjective impairment got worse as the test session progressed.

Subjective reports of the degree of *impairment* caused by symptoms did not differ markedly across the treatment conditions, **Table 3.5.5-3**.

Table 3.5.5-3: Symptom Impairment During Testing[2]

	SYMPTOM				
DRUG CONDITION	DROWSINESS	SLUGGISHNESS	HEADACHE	STOMACH CRAMP	COLD
Granisetron	2.6	2.3	2.2	3.5	
Ondansetron	2.9	3.0	3.0		
Prochlorperazine	2.6	2.3	2.3		
Placebo	2.5	2.9	2.9		2.0

[2] Mean impairment (scale: 2=slight to 5=severe)

Table 3.5.5-3 *con't*: Symptom Impairment During Testing

	SYMPTOM					
DRUG CONDITION	MUSCLE CRAMP	MUSCLE TWITCH	FAINTNESS	DISTURBED VISION	DIZZINESS	GAS
Granisetron				3.0	4.0	3.0
Ondansetron						
Prochlorperazine				2.1		
Placebo						

Delayed symptoms - Symptoms that occurred during the 38 hour period following a drug test session are reported as delayed symptoms. Compared to the placebo condition, headache was reported twice as often in the ondansetron group and one-half as often in the granisetron group - a difference reflecting two subjects and one subject, respectively. Constipation was reported twice as often in the target drug groups when compared to placebo representing a difference of one subject in each case. The *incidence* of delayed symptoms is presented in the following table, **Table 3.5.5-4**.

Table 3.5.5-4: Delayed Symptom Incidence

	SYMPTOM				
DRUG CONDITION	DROWSINESS	SLUGGISHNESS	HEADACHE	CONSTIPATION	DIARRHEA
Granisetron	3 (13%)	4 (17%)	1 (4%)	2 (9%)	1 (4%)
Ondansetron	3 (13%)	3 (13%)	4 (17%)	2 (9%)	
Prochlorperazine	4 (17%)	3 (13%)	2 (8%)	1 (4%)	2 (8%)
Placebo	2 (8%)	2 (8%)	2 (8%)	1 (4%)	

Table 3.5.5-4 *con't*: Delayed Symptom Incidence

DRUG CONDITION	SYMPTOM					
	SWELLING	GAS	NAUSEA	STOMACH CRAMPS	MUSCLE CRAMPS	DISTURBED VISION
Granisetron		1 (4%)	1 (4%)	1 (4%)		
Ondansetron				1 (4%)		
Prochlorperazine	1 (4%)	1 (4%)	1 (4%)			1 (4%)
Placebo	1 (4%)	1 (4%)		1 (4%)	1 (4%)	

Table 3.5.5-4 *con't*: Delayed Symptom Incidence

DRUG CONDITION	SYMPTOM			
	OTHER-SLEPT-A-LOT	OTHER-BRUISING	OTHER-SPACEY	OTHER-DEHYDRATED
Granisetron			1 (4%)	
Ondansetron	1 (4%)			1 (4%)
Prochlorperazine		1 (4%)		
Placebo				

There were small differences in the *severity* of delayed symptoms, reported by subjects, across the three treatment conditions, **Table 3.5.5-4.**

Table 3.5.5-5: Delayed Symptom Severity[3]

DRUG CONDITION	SYMPTOM				
	DROWSINESS	SLUGGISHNESS	HEADACHE	CONSTIPATION	DIARRHEA
Granisetron	2.3	3.7	2.0	3.5	1.0
Ondansetron	2.5	3.0	3.5	4.0	
Prochlorperazine	5.3	3.3	2.5	5.5	
Placebo	4.0	3.0	2.0	2.0	1.5

[3] Mean severity (scale: 1=slight to 7=severe)

Table 3.5.5-5 *con't*: Delayed Symptom Severity

DRUG CONDITION	SYMPTOM					
	SWELLING	GAS	NAUSEA	STOMACH CRAMPS	MUSCLE CRAMPS	DISTURBED VISION
Granisetron		5.0	5.0	5.0		
Ondansetron				7.0		
Prochlorperazine	3.0	4.0	2.0			2.0
Placebo	3.0	3.0		3.0	4.0	

Table 3.5.5-5 *con't*: Delayed Symptom Severity

DRUG CONDITION	SYMPTOM			
	OTHER-SLEPT-A-LOT	OTHER-BRUISING	OTHER-SPACEY	OTHER-DEHYDRATED
Granisetron			3.0	
Ondansetron	3.0			3.0
Prochlorperazine		3.0		
Placebo				

The level of *impairment* associated with delayed symptoms is presented in **Table 3.5.5-6.**

Table 3.5.5-6: Delayed Symptom Impairment[4]

DRUG CONDITION	SYMPTOM				
	DROWSINESS	SLUGGISHNESS	HEADACHE	CONSTIPATION	DIARRHEA
Granisetron	2.33	2.75	2.0	3.0	2.0
Ondansetron	3.3	4.0	3.5	3.0	
Prochlorperazine	3.75	3.0	2.0		
Placebo	3.0	3.0		4.0	

[4] Mean impairment (scale: 2=slight to 5=severe)

Table 3.5.5-6 *con't*: Delayed Symptom Impairment

DRUG CONDITION	SYMPTOM					
	SWELLING	GAS	NAUSEA	STOMACH CRAMPS	MUSCLE CRAMPS	DISTURBED VISION
Granisetron		3.0	2.0	3.0		
Ondansetron				3.0		
Prochlorperazine	2.0		2.0			4.0
Placebo	3.0	3.0		3.0		

Table 3.5.5-6 *con't*: Delayed Symptom Impairment

DRUG CONDITION	SYMPTOM			
	OTHER-SLEPT-A-LOT	OTHER-BRUISING	OTHER-SPACEY	OTHER-DEHYDRATED
Granisetron			2.0	
Ondansetron	2.0			
Prochlorperazine				
Placebo				

After completion of all test sessions, the team physician reviewed symptom reports to assess the probable relationship of each symptom to known or suspected drug effects and side effects. Individual symptom reports by test session were assessed on the following scale: (1) not related; (2) possibly related; (3) probably related; or, (4) definitely related, to the drug condition. As was

anticipated regarding drugs which produce such a low incidence of side effects, most of the symptoms reported by the test subjects were judged to be "not related" or "possibly related" to the treatment condition. None of the reported symptoms were categorized as definitely related to a particular drug condition. Moreover, the incidence of expected side effects such as headache were based on a small number of reports and were judged unamenable to formal statistical treatment.

Finally, each subject was asked to *identify the test session during which they received the positive control drug* (prochlorperazine, 10 mg). Nine subjects were correct in picking the test session during which they received prochlorperazine. Incorrect selections were as follows: six subjects picked the test session when they received the placebo; three picked the session when they received granisetron; two picked the session when they received ondansetron, and four subjects were unable to make a selection. These results are summarized as: nine correct, 11 incorrect, and four no opinion. It is of interest to record the by-day results for the 20 subjects who registered an opinion as to when they received the positive control drug. Six subjects picked the first test session, nine subjects picked the second, three the third and two picked the fourth test day. These results provide evidence of modest success regarding our efforts to select a dose level sufficient to disrupt cognitive performance, but low enough so that neither the subjects nor the investigators would be able to subjectively identify the positive control condition. The fact that the positive control condition produced some alterations in performance but not mood or fatigue also complements evidence regarding the sensitivity of at least two of the Performance Assessment Battery tests (Attention Switching and Unstable Tracking).

4.0 DISCUSSION

Results from this study indicate granisetron and ondansetron are free of troublesome or hazardous side effects and have no apparent effects on cognitive or psychomotor performance - neither causing enhancement nor degradation. Incidents of reported side effects were generally minor / transient and in most cases probably not related to the anti-emetic drugs. There were no serious adverse reactions either during or following testing. Excepting minor problems with indwelling catheters, there were no medical events requiring intervention by the study team physician during or after testing.

In general, the battery of laboratory tests and questionnaires were quite sensitive to fatigue and, to a somewhat lesser extent, were sensitive to the effects of a low dose positive control drug, prochlorperazine (10 mg p.o.). This effect was statistically present as a drug-by-trial interaction across several dependent measures on two of the PAB tests and was in agreement with the serum-drug curve for the positive control condition. Moreover, effects of the positive control drug were generally consistent and in the anticipated direction even when statistical significance was not present. That is to say, scores were generally lower for accuracy and throughput variables while reaction times tended to be of longer duration. Similarly, the results for mood displacement at peak serum-drug levels point toward generally lower scores in the positive control group for affective state change while results related to vigor were unexpectedly mixed.

5.0 CONCLUSIONS

Previous studies have demonstrated granisetron and ondansetron to be clinically safe and effective compounds in the prevention of radiation induced nausea and emesis. This study was designed to assess the effects of these drugs, at clinically relevant doses, on basic cognitive skills and complex task performance. The experimental approach, involving 24 subjects, was a placebo controlled, double blind, crossover design with a positive control condition. Data were collected on cognitive and psychomotor effects, affective state changes, fatigue, temperature, serum-drug levels and adverse events. The drugs of interest (granisetron and ondansetron) were extremely well tolerated with a few reports of generally minor and transient symptoms and without significant effects when compared to the placebo condition. There were no serious adverse events either during the testing or after testing. Also, there were no drug related medical events requiring intervention by the study team physician either during or after the testing. Two of five cognitive tests detected a positive control effect and nearly all or the measurement instruments demonstrated a fatigue effect. There was no evidence of any cognitive, psychomotor or subjective state changes caused by either of the drugs, granisetron or ondansetron. This conclusion is based on the performance measurement techniques described in this report and other techniques may yield different results. These findings support the need for further investigation and a safety validation of the drugs, granisetron and ondansetron, in a complex, operationally relevant task environment. High fidelity flight simulation tests in a weapons systems research simulator are proposed as a follow-on performance evaluation, prior to any final recommendation regarding the use of these drugs under operational military task conditions.

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APPENDIX A
Data Collection Script

DATA COLLECTION SCRIPT

Time	Activity
1630-1645	Subjects arrive (15 min)
1645-1647	Brief overall test and data collection plan (2 min)
1647-1650	Complete *delayed* symptoms checklist #1 (3 min)
1650-1735	Catheter insertions (45 min)
1735-1750	Baseline TRACON (15 min)
1750-1805	Baseline PAB (15 min)
1805-1820	Baseline DSO Analog (15 min)
1820-1822	Baseline vigilance (2 min)
1822-1827	Baseline POMS / VAS (5 min)
1827-1829	Baseline symptoms #6 (2 min)
1829-1830	Baseline subjective fatigue / Baseline temperature (1 min)
1830-1845	Baseline Critical Flicker-Fusion (15 min)
1845-1855	Break / restroom (10 min)
1855-1900	Administer treatment drugs (5 min)
1900-1915	PAB (15 min)
1915-1930	DSO Analog (15 min)
1930-1932	Vigilance (2 min)
1932-1937	POMS / VAS (5 min)
1937-1939	Symptoms checklist #7 (2 min)
1939-1940	Subjective fatigue / Temperature (1 min)
1940-1950	Blood draws (10 min)
1950-2000	Critical Flicker-Fusion (10 min)
2000-2015	PAB (15 min)
2015-2030	DSO Analogue (15 min)
2030-2032	Vigilance (2 min)
2032-2037	POMS / VAS (5 min)
2037-2039	Symptoms checklist #8 (2 min)
2039-2040	Subjective fatigue / Temperature (1 min)
2040-2050	Blood draws (10 min)
2050-2100	Critical Flicker-Fusion (10 min)
2100-2115	PAB (15 min)
2115-2130	DSO Analog (15 min)
2130-2132	Vigilance (2 min)
2132-2137	POMS / VAS (5 min)

2137-2139	Symptoms checklist #9 (2 min)
2139-2140	Subjective fatigue / Temperature (1 min)
2140-2150	Blood draws (10 min)
2150-2200	Critical Flicker-Fusion (10 min)
2200-2215	PAB (15 min)
2215-2230	DSO Analog (15 min)
2230-2232	Vigilance (2 min)
2232-2233	Subjective fatigue / Temperature (1 min)
2233-2300	Critical Flicker-Fusion / TRACON (27 min)
2300-2315	PAB (15 min)
2315-2330	DSO Analog (15 min)
2330-2332	Vigilance (2 min)
2332-2333	Subjective fatigue / Temperature (1 min)
2333-2400	*Feeding* / Critical Flicker-Fusion / TRACON (27 min)
2400-0015	PAB (15 min)
0015-0030	DSO Analog (15 min)
0030-0032	Vigilance (2 min)
0032-0033	Subjective fatigue / Temperature (1 min)
0033-0100	Critical Flicker-Fusion / TRACON (27 min)
0100-0115	PAB (15 min)
0115-0130	DSO Analog (15 min)
0130-0132	Vigilance (2 min)
0132-0137	POMS / VAS (5 min)
0137-0139	Symptoms checklist #10 (2 min)
0139-0140	Subjective fatigue / Temperature (1 min)
0140-0150	Blood draws
0150-0200	Critical Flicker-Fusion (10 min)
0200-0215	PAB (15 min)
0215-0230	DSO Analog (15 min)
0230-0232	Vigilance (2 min)
0232-0233	Subjective fatigue / Temperature (1 min)

APPENDIX B
Performance Assessment Battery

PERFORMANCE ASSESSMENT BATTERY (PAB)

MATRIX ROTATION

Purpose - This task probes the subjects ability to perceive, remember and process spatial information. It is presumed to tap visual short term memory.

Description - This test draws upon 100 basic patterns, each of which, is a 5 by 5 matrix with five illuminated cells that have been selected at random. At the beginning of the trial the subject sees a pattern. The subject studies the pattern and then presses a response key. The pattern is immediately erased and a new one presented. The subject must decide as quickly as possible if the new pattern is identical to the preceding pattern. The subject then presses a designated key for "same" or another designated key for "different." As soon as the response is made, a third pattern appears. The subject must now compare the new pattern to the immediately preceding pattern, etc. For "same" responses, the two patterns are never presented in exactly the same orientation; the second pattern is always rotated either 90 degrees to the left or 90 degrees to the right relative to the preceding pattern. Concurrent verbal suppression tasks have been shown not to affect performance on the Matrix task, supporting the notion this task indeed measures some aspect of spatial information processing.

Sensitivity - Tentative evidence of the sensitivity of this task can be inferred from findings using tests which are likely to load on the same or related spatial factors. For example, the manikin test, a predominately spatial task, is sensitive to the effects of diving to extreme depths. Other test which are similar have been shown to be sensitive to cyclical variations in arousal and the effects of long-term isolation.

CONTINUOUS RECOGNITION

Purpose - One important aspect of higher cognitive function is the ability to maintain attention and to carry out repetitive cognitive processes over time. This test presumes to measure cognitive activities commonly associated with "vigilance."

Description - In this test, the subject is presented with two numbers, one above the other. The task is to remember the bottom number. When the next two numbers are presented, the task is to determine if the new top number is the same as the previous bottom number. However, before responding, the subject must note the new bottom number because as soon as a response is made, the numbers are replaced by a new pair. The subject must not only exercise very short-term memory, but more importantly, must inhibit the response until the new bottom number is committed to memory. The appropriate strategy is to develop a set pattern of observing, memorizing, observing, comparing, and responding. This sequence is different enough from that required by most routine tasks in that it requires constant attention allocation. Even brief lapses result in errors. The task can be made more difficult by requiring the subject to remember and respond to numbers further removed from the immediately preceding one, thus imposing a much higher load on immediate memory.

Sensitivity - This task has a respectable data base indicating sensitivity to both short-term memory and attention allocation. The Continuous Recognition test is known to be sensitive to alcohol and acceleration stress.

MANIKIN AND MATHEMATICAL PROCESSING - ATTENTION SWITCHING

Purpose - In contrast to time sharing described in the above task, this test is designed to probe the subjects ability to shift attention and resource allocation in response to rapidly changing and unpredictable external demands.

Description - The subject has two distinct and discrete tasks to perform. One is a spatially-based task, and the other is a mathematically based test. Each of these appear, trial by trial, simultaneously on the screen. However, an indicator appears at the same time directing the subject to the task that is "active" (i.e., must be responded to). The subject must make a discrete response to the active task. The switching from task to task for each trial is random (within constraints). Therefore, the subject must remember to watch the indicator on each trial, allocate the appropriate resources to respond to that trial and then make the appropriate response. The two tests selected to exercise this paradigm are the Manikin test and the Mathematical Processing test. A manikin "stick figure" is presented facing either forward or backward. In addition, the figure can be either upright or upside-down. The figure is also standing on a box and inside the box is either a rectangle or a circle. In the figure's two hands are a rectangle and a circle. The subject's task is to note which symbol is inside the box, and then to determine which of the manikin's hands is holding the designated symbol. The subject then presses one of two keys, designated left and right, corresponding to the manikin's left or right hand. The second task is Mathematical Processing. When active, a series of three single-digit numbers are presented that must be added or subtracted. If the answer is greater than 5, one response is given. If the answer is less than 5 another response is required.

Sensitivity - The mathematical processing task is likely to be sensitive to stressors that affect working memory. Test sensitivity has been demonstrated for toxic substances, and separately, for caffeine combined with sleep loss.

GRAMMATICAL REASONING - SYMBOLIC

Purpose - This test is designed to assess the subject's ability to manipulate grammatical information, placing demands primarily on working memory. The symbolic grammatical reasoning task is a type of sentence verification task that evaluates general reasoning ability and assesses the processing capacity of working memory

Description - The symbolic grammatical reasoning task is designed to impose variable demands on resources required for the manipulation and comparison of grammatical information. The stimuli consist of sentences of varying syntactic structure accompanied by sets of two or three simultaneously presented symbols (e.g. *, #, and &). The sentences must be analyzed to determine whether they correctly describe the ordering of the characters in the symbol set. Task demand is determined by the amount and complexity of grammatical analysis. This test requires:

(a) the processing of a visual statement consisting of words and symbols, (b) comparing a symbol set to this statement for correctness, (c) holding the result in active memory, (d) processing another visual statement and comparing this with a second symbol set, (e) holding the second result in memory, (f) comparing the results (i.e. both correct, both incorrect, or one correct and one incorrect), (g) pressing a response key to indicate the whether the compared results are the same or different with regard to correctness.

Sensitivity - This test has been demonstrated to be sensitive to the effects of numerous environmental stressors and some drugs.

UNSTABLE TRACKING

Purpose - Tests information processing resources used in the execution of continuous manual control responses. This task is assumed to tap primarily motor output resources, placing minimal demands upon resources associated with input and central processing.

Description - The central characteristic of the Unstable Tracking task is a positive feedback loop responsible for creating instability in the system. Once the system detects a control error, an error velocity is generated, the value of which is determined by operator gain. A fixed target represented by two vertical bars (one above the other) and separated by a vertical space is presented in the middle of the screen and a vertical cursor that moves horizontally through the target is displayed. The subject attempts to maintain the cursor position in the same location as the target by means of a mouse. The built-in instability of the system magnifies any movement of the mouse, therefore, it becomes increasingly difficult to respond to the velocity and position of the cursor.

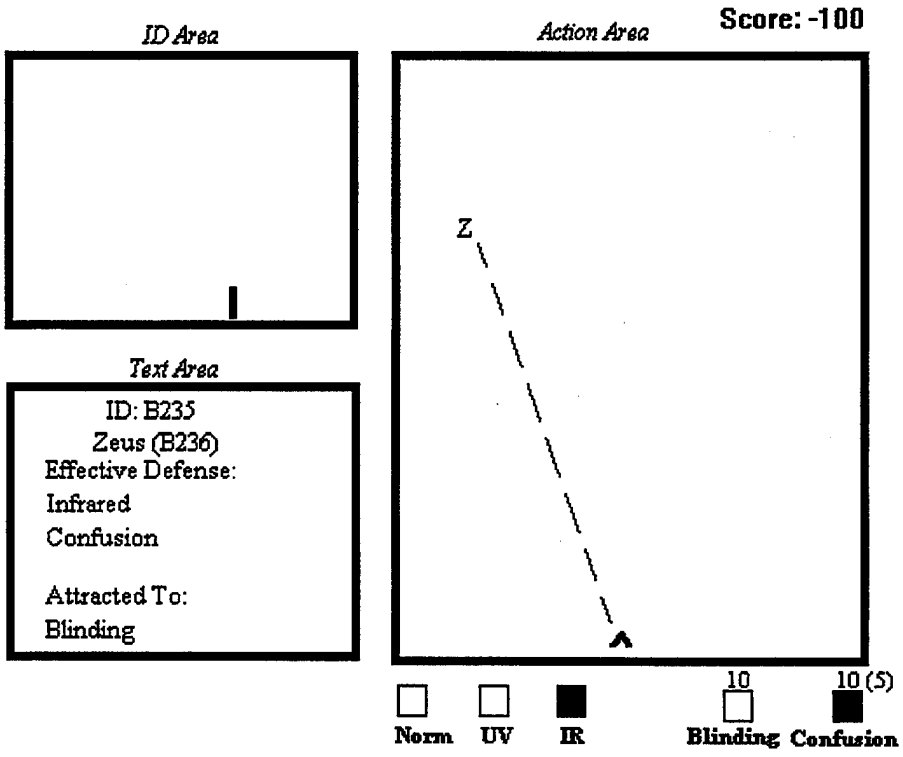
Sensitivity - The Unstable Tracking task has been demonstrated to be sensitive to a variety of stressors to include: alcohol, carbon monoxide, drugs and toxic substances.

APPENDIX C
DSO Analog Task

DSO ANALOG TASK

Overview of Task:

You are a spaceship, and your task is to sneak past as many enemies as possible. Your ship has no offensive capabilities, but has excellent defensive capabilities. As you begin the task, you are located on the right hand screen. Your ship is the indicator at the bottom of the screen. Your enemies appear at the top of the right hand screen, and maneuver down the screen towards you. You are moving forward at a fixed, constant rate. Your forward movement is automatic, and is not within your control. You may, however, move left or right. Each left or right arrow press will move your ship slowly left or right. In order to continue moving in a chosen direction, you must allow your ship to come to a stop before pressing the key again. Holding down the arrow key constantly, as well as pressing the key in a quick repetitive fashion will not increase your speed.



There are three separate areas in this task. The largest, on the right side, is the Action Area. The Action Area is the screen that will display the indicator representing your ship. The top screen on the left side is called the ID Area. As your enemy appears on the right side, a bar signifying its presence appears in the ID Area. One bar appears for every threat displayed in the Action Area. The bottom screen on the left side is called the Text Area. Relevant information will appear in the Text Area regarding the selected bogie.

Defenses:

There are two types of defense mechanisms that may be used: long- and short-term. Once they are initiated, the indicator light located beneath the Action Area changes color to signify its use.

There are three types of long-term invisibility strategies that may be utilized anytime during your task. Once initiated, an invisibility strategy will last indefinitely. One long-term invisibility strategy may be used at a time. They are: normal invisibility (NORM), ultraviolet invisibility (UV), and infrared invisibility (IR).

There are two types of short-term strategies that may be utilized in combination with the long-term strategies: Confusion and Blinding. There are 10 of each strategy available. The defense will last 5 seconds each time it is used. The time, however, may be "stretched" by clicking a second time on a short-term strategy that is already running. The total time will be increased to 5 seconds again. The number directly above the short-term indicator represents how many defense mechanisms of that type remain available; the number in parenthesis next to it appears as a "countdown clock" once the strategy is initiated.

Both long- and short-term strategies are initialized by clicking on the desired strategy in the text screen. An enemy must be selected in order to display the most relevant strategy against it. Note that the indicator lights on the bottom right of the screen (underneath the Action Area) can not be "pushed." They simply light up when a particular defense has started. To activate a defense you must click in the Text Area.

Procedure for initializing a defense strategy:

1. Select the enemy

This can be done either by clicking on the corresponding bar in the ID Area, or by clicking on enemy in the Action Area. Once an enemy is selected, the corresponding bar in the ID Area changes color and a circle appears around the corresponding threat in the Action Area. In addition, only information regarding the relevant defense strategy for that enemy appears in the Text Area. One enemy may be selected and displayed at a time.

2. Initialize the defense

This can be done by clicking on the desired defense in the Text Area. Once a long-term defense is chosen, any previous long-term defense that was in force is terminated and the new defense is effective. For example, if you are currently running NORM invisibility and you click on IR, the NORM defense will turn off and the IR defense will turn on. Once a short-term defense is

chosen, it will remain on for the total of 5 seconds. Again, it may be used in combination with any other defense mechanism.

Enemies:

The following table lists the enemies you will be fighting (You do not need to memorize or learn the table; it is simply to give you some general information about the enemies). The first two columns describe the name and the ID. The ID is what you will see on the Action Area of the screen (note the "Z" on the Action Area of the figure). There are three different types of enemies: Mobile Ships, Missiles, and Stationary Finders. Recall that you are always moving forward, so all enemies will appear to be moving toward you (even the Finders). Ships and Finders can laser you or launch missiles at you. Missiles can explode on you.

No enemy can see past its range. As a point of reference, the Action Area is 1000 units long and 1000 units wide. When an enemy can not see you (i.e., if it is out of range or you are correctly defending against it) it enters "Search Mode" which is a slow criss-cross pattern, looking for you. Note that only Missiles and Ships exhibit this characteristic movement; Finders can not move so they will always be "stationary." When an enemy locks onto you it enters "Track Mode" which means the enemy comes right at you, attacking.

Name	ID	Type	Range
Zip-Zap	ZZ	Mobile Ship	400
Find-Kill	FK	Missile	350
Whiner	W	Stationary Finder	700
Watermellon	WM	Missile	400
Big K	BK	Missile	500
Small and Light	SL	Mobile Ship	700
Big J	BJ	Stationary Finder	750
Zeus	Z	Mobile Ship	700
Codeine	C	Mobile Ship	700
Screamer	S	Missile	300
String Bean	SB	Mobile Ship	600
Coke Creamer	CC	Stationary Finder	750

Additional DSO Task Information:

Within the Text Area:

Effective Defense: Most bogies have one effective long-term defense that enables you to remain invisible. They cannot attack you as long as this defense is on. In addition, there may be short-term defense that also allow you to effectively defend against the threat.

Attracted To: There are certain long- and short-term mechanisms that enable a bogie to locate you. If these are implemented, the bogie will be able to attack you. Example: You are

running Infrared as an effective defense against Bogie 1, who is attracted to Confusion. Bogie 2's effective defenses are both Ultraviolet and Confusion. You maintain Infrared as your long-term defense, and initiate Confusion in order to ward off Bogie 2. Bogie 1 can now attack you due to its attraction to Confusion, in spite of the Infrared protection. This attack may last up to 5 seconds, which is the time limit for Confusion.

ID Number: Once a threat is selected, an ID number is displayed on the first line of the Text Area. This number (in blue) is the true ID of the enemy. The signal reference (in red) is displayed on the second line.

Identification of Enemy:

There is a chance that the enemy will be misidentified.

In order to confirm the correct identification of an enemy, the signal reference is compared to the true ID of the enemy. It should be evaluated on the following points: Every bogie has one unique ideal identification. These are given in your information strip located above the function keys of your keyboard. The alpha character in the enemy ID corresponds to its placement in the ID Area (R for right side, L for left side, T for top, and B for bottom). The three numerics following the alpha character of the signal reference will come within 15 points of the true ID located above it. If it does not, it is misidentified and its Text Area information will be incorrect, as well as its display in the Action Area. If the misidentified enemy is left uncorrected, you may choose the wrong defense based on the information in the Text Area.

To correct a misidentified threat, select it (either from the ID or Action Areas), press the I key (or TAB key) to initialize the identify sequence, and press the function key that corresponds to the threat you have decided is correct. Example: A true ID (first ID located in the Text Area) for a selected enemy whose bar signal in the ID Area is on the bottom is B40. The signal reference is T100. The signal is incorrect because 1) the alphas do not correspond, and 2) the numeric value is more than +/- 15 points. It should therefore be changed in order to reveal the correct text information. Press I (or TAB key). Press F7. [Pressing I/TAB key begins the ID process, and F7 corresponds to the identification that comes within +/- 15 points of the true ID (B40).]

Scoring:

10 points are lost every time a laser is fired and hits your spaceship. 100 points are lost every time a missile explodes on your spaceship (missiles are identified as WM, FK, S, and BK). 30 points are lost every time a misidentified ship is allowed to pass you. 50 points are gained every time your spaceship is passed by a correctly identified threat in the Action Area.

APPENDIX D
Symptoms Checklist

SYMPTOMS CHECKLIST

Subject number ____ **Date _____**

Time _____

Please circle below if any of the symptoms apply to you right now. If you answer YES, circle the number which best describes the degree of the symptom.

			Slight						Severe
1. Headache	No	Yes	1	2	3	4	5	6	7
2. Dizziness	No	Yes	1	2	3	4	5	6	7
3. Drowsiness	No	Yes	1	2	3	4	5	6	7
4. Sluggishness	No	Yes	1	2	3	4	5	6	7
5. Faintness	No	Yes	1	2	3	4	5	6	7
6. Numbness	No	Yes	1	2	3	4	5	6	7
7. Tingling	No	Yes	1	2	3	4	5	6	7
8. Hot	No	Yes	1	2	3	4	5	6	7
9. Cold	No	Yes	1	2	3	4	5	6	7
10. Sweating	No	Yes	1	2	3	4	5	6	7
11. Rash	No	Yes	1	2	3	4	5	6	7
12. Itching	No	Yes	1	2	3	4	5	6	7
13. Swelling	No	Yes	1	2	3	4	5	6	7
14. Gas	No	Yes	1	2	3	4	5	6	7
15. Indigestion	No	Yes	1	2	3	4	5	6	7
16. Nausea	No	Yes	1	2	3	4	5	6	7
17. Diarrhea	No	Yes	1	2	3	4	5	6	7
18. Constipation	No	Yes	1	2	3	4	5	6	7
19. Stomach Cramps	No	Yes	1	2	3	4	5	6	7
20. Muscle Cramps	No	Yes	1	2	3	4	5	6	7
21. Muscle Twitching	No	Yes	1	2	3	4	5	6	7
22. Muscle Weakness	No	Yes	1	2	3	4	5	6	7
23. Trembling	No	Yes	1	2	3	4	5	6	7
24. Irregular Breathing	No	Yes	1	2	3	4	5	6	7
25. Irregular Heartbeat	No	Yes	1	2	3	4	5	6	7
26. Disturbed Vision	No	Yes	1	2	3	4	5	6	7

27. Other ( )	No	Yes	1	2	3	4	5	6	7
28. Other ( )	No	Yes	1	2	3	4	5	6	7
29. Other ( )	No	Yes	1	2	3	4	5	6	7
30. Other ( )	No	Yes	1	2	3	4	5	6	7

For each symptom marked "Yes", do you think the symptom was caused by the test drug?

Symptom Name and #	Yes	No	If No, Likely Cause?

To what extent would the symptom(s) marked "yes" impair your ability to perform normally assigned military tasks to include driving to and from work?

Impairment	Symptom #	Symptom #	Symptom #	Symptom #	Symptom #
Severe					
Major					
Moderate					
Slight					
None					

Which treatment do you think you were given?

Anti-Emetic Test Drug	
Positive Control Drug	
Placebo	

STOP

TO BE COMPLETED BY PHYSICIAN / INVESTIGATOR

Physician's assessment of cause

Related to Drug:	Symptom #___	Symptom #___	Symptom #___	Symptom #___	Symptom #___
Definitely					
Probably					
Possibly					
Not					
Other (explain)					

Treatment drug- check block (to be completed by investigator/medical monitor)

A	B	C	D

APPENDIX E
Activity Log

A C T I V I T Y   L O G

Number ______________________

PLEASE INDICATE DATE

T I M E   O F   D A Y   (LOCAL)

DATE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
SLEEP/NAP TIME																								
SUBJECTIVE FATIGUE																								
Temperature																								

DATE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
SLEEP/NAP TIME																								
SUBJECTIVE FATIGUE																								
Temperature																								

DATE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
SLEEP/NAP TIME																								
SUBJECTIVE FATIGUE																								
Temperature																								

DATE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
SLEEP/NAP TIME																								
SUBJECTIVE FATIGUE																								
Temperature																								

SUBJECTIVE FATIGUE

Write the number of the statement which describes how you feel RIGHT NOW.

1 = Fully alert, Wide Awake, Very Peppy
2 = Very lively, Responsive, Not at Peak
3 = Okay, Somewhat Fresh
4 = A Little Tired, Less Than Fresh
5 = Moderately Let Down
6 = Extremely Tired
7 = Completely Exhausted, Unable to function

Indicate Periods of Sleep of Sleep to nearest 1/2 hour by:
S-----S at start and end of sleep period.

UPON AWAKENING, INDICATE SLEEP QUALITY WITH :

+ TO INDICATE THAT YOU SLEPT BETTER THAN NORMAL
= TO INDICATE THAT YOU SLEPT ABOUT THE SAME AS NORMAL
- TO INDICATE THAT YOU SLEPT WORSE THAN NORMAL

APPENDIX F
Serum-Drug Levels

SERUM-DRUG LEVELS

Subject	Draw	Granisetron	Ondansetron	Prochlorperazine
		ng/ml	ng/ml	pg/ml
1	1	0.79	23.80	55.30
1	2	2.63	37.40	163.00
1	3	2.14	35.60	225.00
1	4	1.50	16.00	150.00
2	1	0.57	**1.75**	**46.70**
2	2	1.93	15.50	162.00
2	3	4.03	14.40	287.00
2	4	1.97	7.28	766.00
3	1	0.92	3.81	235.00
3	2	1.31	11.20	352.00
3	3	4.51	11.00	342.00
3	4	2.47	4.40	425.00
4	1	5.76	7.37	294.00
4	2	5.64	10.60	533.00
4	3	8.64	13.30	415.00
4	4	6.30	6.70	390.00
5	1	8.46	3.00	292.00
5	2	7.72	24.10	477.00
5	3	9.56	28.70	608.00
5	4	6.60	10.40	756.00
6	1	4.37	7.20	87.40
6	2	5.95	28.40	373.00
6	3	7.98	28.90	591.00
6	4	4.91	16.20	588.00

Subjet	Draw	Granisetron	Ondansetron	Prochlorperazine
		ng/ml	ng/ml	pg/ml
7	1	1.48	**<2**	274.00
7	2	5.53	**<2**	755.00
7	3	4.63	**<2**	805.00
7	4	3.35	**<2**	638.00
8	1	**<0.2**	7.50	118.00
8	2	**<0.2**	15.60	280.00
8	3	**<0.2**	10.90	448.00
8	4	**<0.2**	3.00	884.00
9	1	2.15	19.32	158.00
9	2	7.83	33.19	602.00
9	3	15.53	27.57	458.00
9	4	9.09	17.36	416.00
10	1	**<0.2**	**<2**	**<50**
10	2	3.44	**<2**	329.00
10	3	4.48	24.30	347.00
10	4	1.08	**<2**	204.00
11	1	**<0.2**	**<2**	72.00
11	2	2.13	6.70	**<50**
11	3	3.02	22.20	1511.00
11	4	2.52	**n/s**	861.00
12	1	7.95	**<2**	**<50**
12	2	11.62	3.88	213.00
12	3	9.25	25.50	644.00
12	4	6.74	18.90	2521.00
13	1	0.81	20.60	102.00
13	2	3.07	32.70	599.00
13	3	2.73	26.20	915.00
13	4	**<0.2**	14.20	782.00

Subject	Draw	Granisetron	Ondansetron	Prochlorperazine
		ng/ml	ng/ml	pg/ml
14	1	0.54	**<2**	**<50**
14	2	4.34	6.73	**<50**
14	3	3.32	13.00	54.00
14	4	2.33	13.00	85.00
15	1	**0.14**	18.40	**<50**
15	2	1.07	23.00	272.00
15	3	2.88	20.00	103.00
15	4	3.69	13.40	95.00
16	1	1.21	**<2**	81.30
16	2	2.63	15.90	66.90
16	3	3.27	15.40	**<50**
16	4	1.99	7.80	**<50**
17	1	10.50	**<2**	425.00
17	2	16.30	**1.73**	584.00
17	3	22.20	20.82	564.00
17	4	15.70	2.14	1292.00
18	1	6.46	8.44	705.00
18	2	7.75	8.94	1081.00
18	3	9.72	7.90	1125.00
18	4	7.90	4.79	1463.00
19	1	4.53	**<2**	624.00
19	2	7.91	15.07	552.00
19	3	5.31	12.03	545.00
19	4	3.81	4.58	265.00
20	1	2.96	11.40	423.00
20	2	6.28	19.00	403.00
20	3	7.73	19.50	702.00
20	4	3.11	15.40	1181.00

Subject	Draw	Granisetron	Ondansetron	Prochlorperazine
		ng/ml	ng/ml	pg/ml
21	1	**<0.2**	7.76	64.70
21	2	4.11	36.20	83.50
21	3	7.07	29.37	1440.00
21	4	2.56	**<2**	3075.00
22	1	**<0.2**	5.04	**<50**
22	2	2.83	16.62	**<50**
22	3	4.07	20.23	**<50**
22	4	4.07	9.70	451.00
23	1	**<0.2**	7.21	271.00
23	2	0.56	20.91	368.00
23	3	1.19	19.20	518.00
23	4	**<0.2**	9.96	495.00
24	1	**<0.2**	**<2**	**<50**
24	2	2.64	21.43	**<50**
24	3	5.45	19.76	119.00
24	4	4.15	10.66	693.00